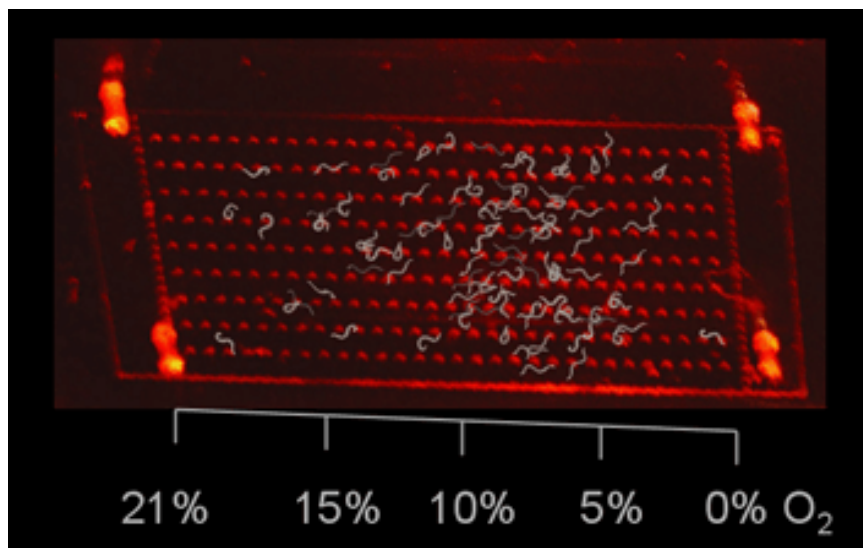


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## Worms May Seek Comfortable Atmosphere for Dining



**Image Title:** Worms in an oxygen gradient avoid both high and low concentrations of oxygen, clustering where the concentration is between five and ten percent. - Laboratory of Cornelia I. Bargmann

Researchers have discovered the molecular mechanisms by which the roundworm *C. elegans* senses oxygen concentrations in the highly variable soil environment where it lives. The researchers theorize that the worm may select feeding environments - regions where there are high concentrations of tasty bacteria - because they have a more comfortable low oxygen concentration that is created by oxygen-consuming bacteria.

The researchers theorize that the oxygen-sensing mechanism they have discovered may also exist in animals that must avoid low-oxygen environments, such as fish. Furthermore, they speculate that a similar mechanism may exist in humans to trigger hyperventilation during exercise or exposure to anoxic environments.

The research teams, led by Howard Hughes Medical Institute investigator Cornelia Bargmann and colleague Michael Marletta, published their findings June 27, 2004, in the early online edition of the journal *Nature*. Bargmann

and her colleagues are at the University of California, San Francisco, and Marletta and his colleagues are at the University of California, Berkeley. Joint lead authors of the paper are Jesse Gray in Bargmann's laboratory and David Karow in Marletta's laboratory. Other co-authors are from the University of Michigan and the University of Medicine and Dentistry of New Jersey.

According to Bargmann, previous research had indicated that *C. elegans* responds to low oxygen concentrations, but essentially nothing was known about how the animals sense the oxygen. "We know almost nothing about the oxygen-sensing mechanisms in such animals as *C. elegans*, because we have all the prejudices of land animals," she said. "We are immersed in a 21 percent oxygen atmosphere all the time, and our blood stream and lungs maintain the optimum oxygen levels in our tissues. So we take oxygen levels for granted. But most other animals on the planet live in water or the soil, such as *C. elegans*. And since oxygen diffuses much more slowly in those environments, they must evolve ways to sense oxygen and react to changes in oxygen levels."

To measure the worms' response to oxygen gradients, co-author Hang Lu, an engineer who works in Bargmann's laboratory, designed and constructed a tiny chamber in which oxygen gradients could be precisely controlled. Their initial behavioral studies in the chambers confirmed that the worms avoided low-oxygen environments. Surprisingly, though, the animals also avoided high-oxygen environments.

To explore the animals' oxygen sensing, the researchers drew on past research in the Marletta laboratory on molecules called guanylate cyclases, which were known to sense nitric oxide in animals, as needed for the regulation of blood-vessel relaxation. Although the researchers discovered the same type of molecules in *C. elegans*, they could find no evidence that they were sensing nitric oxide, said Bargmann.

By mapping the expression of the guanylate cyclase genes, the researchers found that they were active in sensory neurons of the worms. Since the worms responded behaviorally to oxygen, the researchers reasoned that it might be this response that the guanylate cyclases were mediating. Further support for this idea came from their finding that the guanylate cyclase protein GCY-35 bound to molecular oxygen, via an iron-containing heme structure similar to that found in hemoglobin.

When the researchers removed the gene for GCY-35 in worms, they found that the knockout animals still avoided low oxygen, but no longer moved away from areas of high oxygen - suggesting that GCY-35 governed response to high oxygen levels.

What's more, when the researchers knocked out the genes for the sensory transduction channels through which the guanylate cyclase proteins exert their effects on neurons, these mutant animals also failed to avoid high-oxygen environments.

In behavioral studies, the researchers found that oxygen levels regulated an aggregation behavior in the animals. And when they performed the behavioral experiments in the presence of bacteria, they found that higher oxygen levels triggered social feeding, in which the worms would aggregate around concentrations of bacteria. The researchers observed that these clusters of bacteria, or bacterial lawns, consumed oxygen more quickly than it could diffuse into the area, thereby reducing oxygen levels.

“The first thing we showed was that oxygen regulates this aggregation behavior, which fits our model,” said Bargmann. “Then we reasoned that since bacteria are incredible oxygen hogs, that it's just that the food is consuming oxygen faster than oxygen can diffuse in. So, oxygen sensing may be a hunting strategy. It's like smelling your food, except it's actually smelling the activity of the food.” Bargmann emphasized that seeking a lower oxygen environment could represent a protective response against levels of oxygen that could be damaging to the worms.

Further studies will include searching for similar oxygen-sensing mechanisms in animals such as fish that must cope with low oxygen levels in water, said Bargmann. The mechanism may even exist in humans, she said.

“We do monitor oxygen levels in our bloodstream using a rice grain-sized organ called the carotid body that sits at the fork of the carotid artery,” said Bargmann. “When there's even a small drop in oxygen concentration, as might happen in vigorous exercise, these neuron-like cells evoke a hyperventilation or rapid-breathing response. Little is known about this mechanism, and it might well be that we use a similar oxygen-sensing mechanism as the roundworm,” she said.