The Mind of a Male?
Dmitri B. Chklovskii and Cornelia I. Bargmann
Science **337**, 416 (2012);
DOI: 10.1126/science.1225853

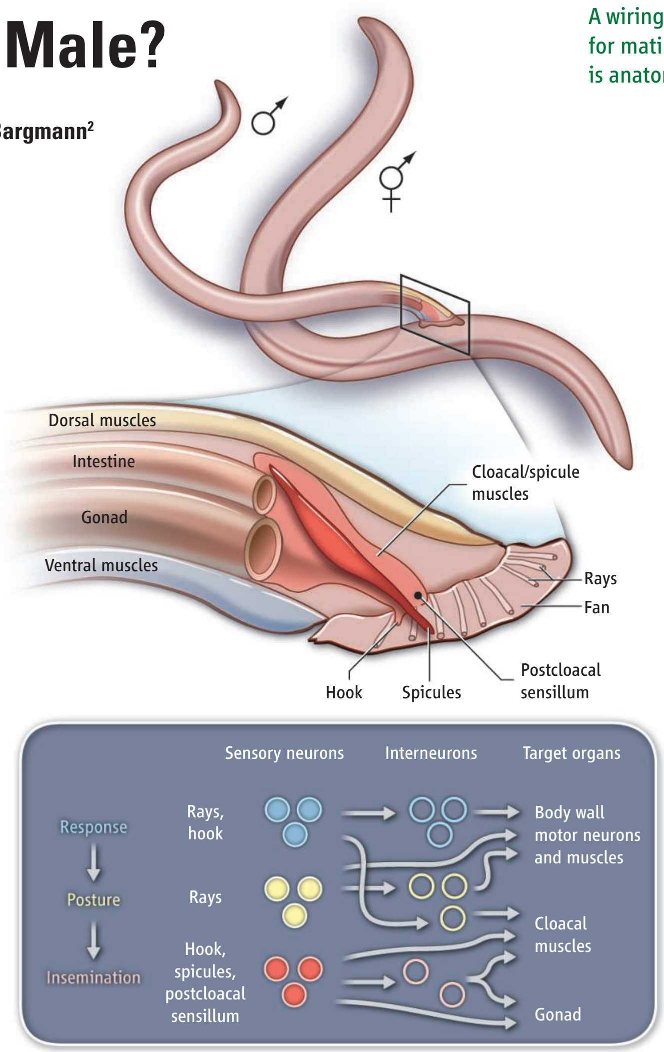
NEUROSCIENCE

The Mind of a Male?

A wiring diagram of neuronal circuits for mating behaviors in the male worm is anatomically reconstructed and analyzed.

Dmitri B. Chklovskii[1] and Cornelia I. Bargmann[2]

When a major computer chip manufacturer brings a new integrated circuit to the market, its competitors often rush to reverse-engineer the chip to understand how it works. They shave off thin layers of the semiconductor material while imaging each newly revealed surface under an electron microscope. By tracing the wires in the electron micrographs, computer engineers assemble the wiring diagram of the chip, which allows them to eventually deduce its function. Similarly, neuroscientists hope to gain insights into the way the nervous system generates behavior by reconstructing its wiring diagram. Like the solid-state wires in computer chips, biological "wires" that carry electrical signals are tens of nanometers in diameter, requiring electron microscopes and ultrathin sectioning to image them. On page 437 of this issue, Jarrell *et al.* (*1*) use this approach to reconstruct the nervous system in the tail of a male *Caenorhabditis elegans* roundworm.



The mating circuit. The mating structures in the tail of the male worm *C. elegans* are shown. The colors correspond with a simplified summary of the neuronal circuits that control the indicated mating behaviors.

Why did they choose this seemingly exotic circuit to reconstruct? *C. elegans* is less than 1 mm long, and the subsystem in question contains only 170 neurons and 64 muscles, making complete reconstruction possible. Yet the mating behavior of the *C. elegans* male is considered the most complex innate behavior of the animal and has interesting decision-making features (*2*). Previous circuit reconstructions of *C. elegans* hermaphrodites (essentially females) (*3*, *4*) showed that their wiring is largely stereotyped, allowing comparisons between individuals and sexes. The male worm chosen for reconstruction was fixed and sectioned decades ago, by the same group that performed the early hermaphrodite reconstructions (*4*); this choice aids comparisons and also hints at the element of black magic that still characterizes sample preparation for electron microscopy.

The elementary building blocks of the nervous system are neurons and synapses. A *C. elegans* male has 383 neurons, compared to 302 in the hermaphrodite; nearly all male-specific neurons are associated with a delicate, fan-shaped mating structure in the tail (see the figure). Accordingly, the tail reconstruction encompasses 81 male-specific neurons as well as 89 neurons that are shared by both sexes. Neurons are classified as sensory neurons based on specialized externally directed structures, as motor neurons if they mainly synapse onto muscles or the gonad, or as interneurons if they mainly form synapses with other neurons. Most male-specific neurons are sensory neurons (52 in the reconstruction); the interneurons are a mix of male-specific and shared, and motor neurons are mostly shared between sexes. This cellular division suggests that mating decisions are driven by specialized sensory input.

Synapses fall into two classes: those that use chemical neurotransmitters to signal between neurons, and gap junctions that form electrical connections between two cells. Chemical synapses are intrinsically directed, whereas gap junctions can be symmetrical or asymmetric. The male tail has as many reconstructed synaptic connections as the entire hermaphrodite nervous system, with a slightly stronger bias toward gap junctions (28% versus 19%). The wiring from start to finish is remarkably compact: About half of the synapses onto muscles come directly from sensory neurons, and most neurons are only one synapse away from a muscle or the gonad. The dominant direction of the synapses is feedforward, from sensory neuron toward muscle. This directionality is supplemented by synapses between different classes of sensory neurons, potentially bidirectional gap junctions, and limited feedback from interneurons.

The wiring diagram of a nervous system can be represented by a graph whose nodes are neurons or muscle, and whose edges are synapses. Jarrell *et al.* reconstruct this graph for the male wiring diagram. Rather than merely counting the number of synapses, as was previously done for the hermaphrodite, they estimate the strength of connections by taking their total size (which can vary by a factor of 100) into account. They then use the graph to formulate both concrete and abstract hypotheses about the logic of the mating circuit. At a concrete level, they identify five modules, or highly connected groups of neurons, and suggest mating-related behaviors that the modules might control: the response to hermaphrodite contact, locomotion, posture (two modules), and insemination. At an abstract level, they analyze the reconstructed wiring diagram using the tools of network science (*5*): They report degree

[1]Howard Hughes Medical Institute, Janelia Farm Research Campus, Ashburn, VA 20147, USA. [2]Howard Hughes Medical Institute, The Rockefeller University, New York, NY 10065, USA. E-mail:cori@mail.rockefeller.edu; chklovskiid@janelia.hhmi.org

CREDIT: B. STRAUCH/SCIENCE

Published by AAAS

and connection strength distributions, find that the network is small-world, and identify its community (module) structure. They find overrepresented connectivity motifs among connected triplets of neurons, including feed-forward motifs, which are also common in the hermaphrodite wiring diagram (*6*, *7*) and the mammalian cortex (*8*). The broad statistical similarity between these graphs and those reported for the mammalian cortex (*8*, *9*) suggests that fundamental principles of circuit operation gleaned from the worm may help us understand how mammalian brains generate behavior.

The challenge going forward is to convert the reconstruction into detailed knowledge of circuit function. First is the question of what the neurons (nodes) do. Of the 302 neurons of the hermaphrodite, functions are known for about 60%; 30% have also been characterized by functional calcium imaging, and 15% by electrophysiological recordings—a respectable fraction of the nervous system. For many male-specific neurons, functions remain to be assigned, and the neuronal activity patterns are unknown. Moreover, in the new reconstructions, two-thirds of the neurons that males share with hermaphrodites are strongly sexually dimorphic in their wiring, which suggests that the male worm is a new animal whose neurons cannot be assumed to have the same functions as those of his sisters (*10*).

At the circuit level, an anatomically reconstructed wiring diagram leaves many unanswered questions about synapses (edges). For example, electron micrographs do not reveal whether a chemical synapse is excitatory or inhibitory, or whether an electrical synapse is asymmetric or symmetric. Information about these properties and about neuronal dynamics is essential for understanding circuits, even for simple elements such as the feedforward motif. An anatomical map of synapses also fails to show neuromodulators that act at a distance, which play important roles in modifying functional connectivity between neurons. Which of these "nonanatomic" features are necessary to understand circuit function? The importance of the complete reconstruction is the ability to pose this question in a rigorous way. With advances in quantitative microscopy and genetically encoded sensors, it seems increasingly feasible to examine neuronal activity during mating behavior; such measurements would reveal whether attractor networks, perceptrons, and other models for circuit function are embodied in the male nervous system.

References

1. T. A. Jarrell *et al.*, *Science* **337**, 437 (2012).
2. K. S. Liu, P. W. Sternberg, *Neuron* **14**, 79 (1995).
3. L. R. Varshney, B. L. Chen, E. Paniagua, D. H. Hall, D. B. Chklovskii, *PLOS Comput. Biol.* **7**, e1001066 (2011).
4. J. G. White, E. Southgate, J. N. Thomson, S. Brenner, *Philos. Trans. R. Soc. London Ser. B* **314**, 1 (1986).
5. M. E. J. Newman, *Networks: An Introduction* (Oxford Univ. Press, Oxford, 2010).
6. R. Milo *et al.*, *Science* **298**, 824 (2002).
7. M. Reigl, U. Alon, D. B. Chklovskii, *BMC Biol.* **2**, 25 (2004).
8. S. Song *et al.*, *PLoS Biol.* **3**, e68 (2005).
9. O. Sporns, R. Kötter, *PLoS Biol.* **2**, e369 (2004).
10. K. Lee, D. S. Portman, *Curr. Biol.* **17**, 1858 (2007).

10.1126/science.1225853

MATERIALS SCIENCE

A Roadmap for the Assembly of Polyhedral Particles

How particles pack together as a solid can often be predicted just from their shape and how many neighbors they have in the fluid phase.

Joost de Graaf[1] and Liberato Manna[2,3]

Self-assembly of atomic, molecular, or artificial nanoscale units into superstructures is a prevalent topic in science. Advances in control over the synthesis of colloidal nanoparticles (*1*, *2*), in their organization into ordered structures (*3*–*7*), and in modeling of assembly (*8*–*10*) have boosted interest in this topic. Yet predicting what types of superstructures will be formed from specific building blocks according to the shape of the blocks and their interactions remains an open problem (*11*). Even if the shape is spherical and interactions between blocks do not depend on their mutual orientation, one cannot model the finite-pressure assembly on the basis of simple close-packing arguments; more elaborate approaches are required. On page 453 of this issue, Damasceno *et al.* (*12*) report the most extensive and systematic study thus far on the assembly behavior of polyhedral "hard" particles of many different shapes. The study exploits a large set of shapes to determine simple predictive criteria for assembly.

Modeling anisotropic hard-particle assembly began many decades ago. In 1949, Onsager predicted that hard cylinders with hemispherical caps (spherocylinders) spontaneously form a nematic liquid crystal past a threshold in volume fraction (*13*). The organization is driven by maximization of the configurational space that is made available to the particles (in other words, a maximization in the positional and orientational entropy of each cylinder). This assembly works best when spherocylinders are organized parallel to each other.

For hard particles with flat facets, entropy maximization favors mutual alignment of particles along these facets (*14*). This requirement translates into directional interactions of each particle with its neighbors [so-called "directional entropic forces" (*14*)]. The concept of directional entropic forces is similar to the directional bonding between atoms in solids, and the connection is exploited by Damasceno *et al.* to draw parallels between the results of their calculations for hard particles and the types of bonds found in solids.

Slow compression of particles from the fluid phase, as done in these calculations, mimics the assembly of colloidal nanoparticles by controlled evaporation of the solvent in which they are dissolved—a process that steadily increases the volume fraction of particles. The calculations show that, depending on their initial shape, hard polyhedra will assemble in one of four ways. They can form crystals (ordered structures in which units are positionally and orientationally blocked at their sites), plastic crystals (ordered structures in which units are free to rotate but remain positionally fixed at their sites), liquid crystals (structures that have positional disorder but have a strong orientational order), or fully disordered structures.

Some of the individual results of the simulations are unexpected. For example, square pyramids first assemble into cubes and then into sheared cubic lattices—a case of hier-

[1]Soft Condensed Matter, Debye Institute for Nanomaterials Science, Utrecht University, 3584 CC Utrecht, Netherlands. [2]Istituto Italiano di Tecnologia, 16145 Genova, Italy. [3]Kavli Institute of NanoScience, TU Delft, 2628 CJ Delft, Netherlands. E-mail: liberato.manna@iit.it; j.degraaf1@uu.nl