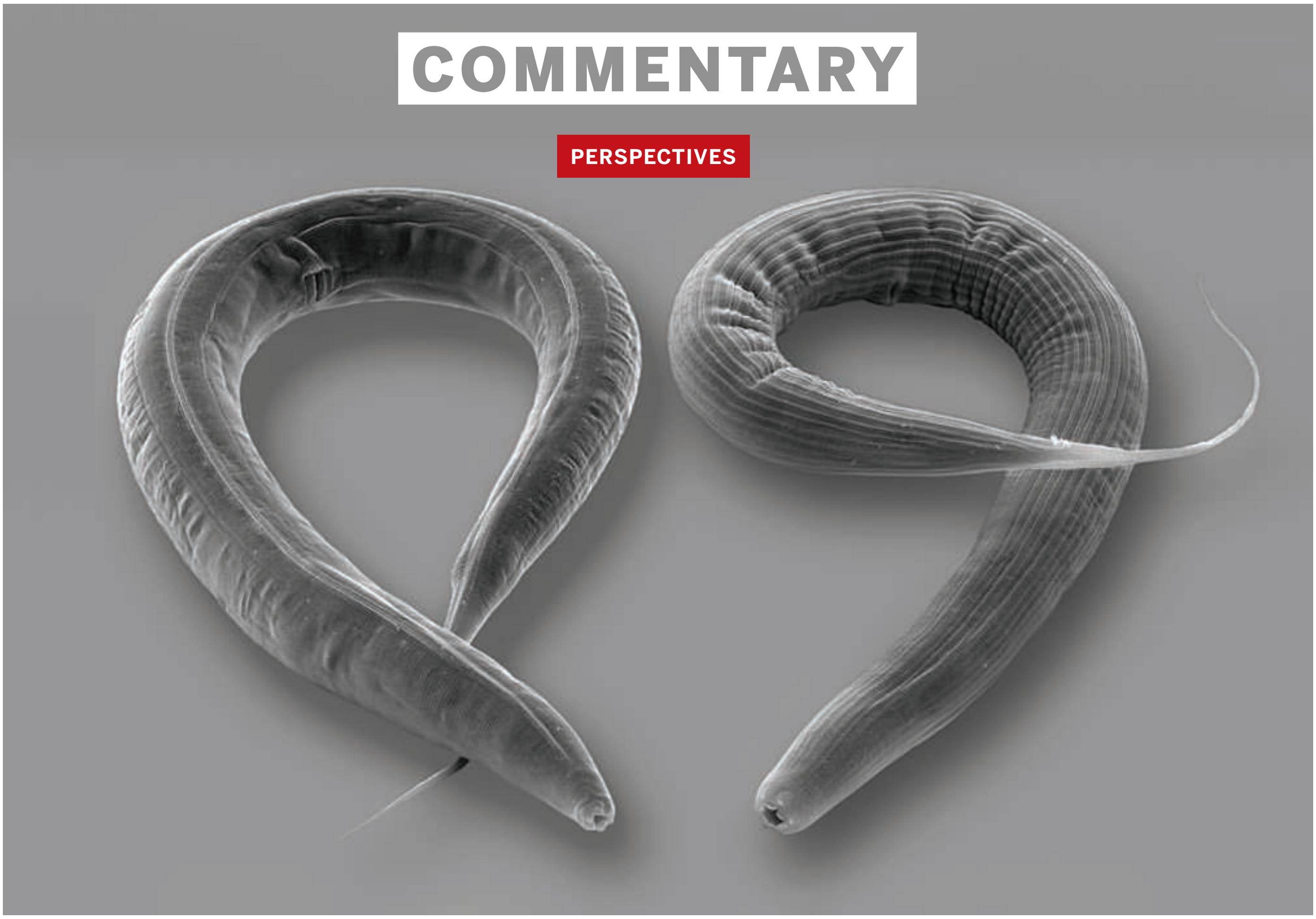

Although they share a common ancestor, *Caenorhabditis elegans* (left) feeds exclusively on bacteria, whereas *Pristionchus pacificus* (right) can also engage in predatory behavior.

IMAGE: RALF SOMMER/MAX PLANCK INSTITUTE FOR BIOLOGY TÜBINGEN

NEUROSCIENCE

The mind of a predatory worm

Widespread neural connectivity changes underlie a behavioral switch between worm species

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Connectomics, the detailed mapping of synaptic connections in neural circuits or entire brains, holds the promise of understanding the basis of how neural networks process information (network computation) and produce behavior. Comparing the connectomes of different species extends this promise by relating differences in connectomes to differences in behavior. When it comes to connectomes of complete nervous systems, the nematode worm *Caenorhabditis elegans*, with its nervous system of 302 neurons, has always had a trailblazing role. It was for this worm that the first complete connectome of a nervous system of an entire animal was reconstructed from electron microscopy images in 1986 (*1*). On page 476 of this issue, Cook *et al.* (*2*) report a comparison between the complete connectomes of two related species of nematode worm: *C. elegans* and the predatory *Pristionchus pacificus*. The findings suggest that behavioral differences between the species are not just based on a single change but result from alterations to synaptic connections, growth patterns, and cell death.

The 1986 *C. elegans* connectome proved invaluable for neurobiological research in the worm and for circuit neuroscience in general (*1*, *3*). Yet despite the knowledge of all connections, new and unexpected network computations and behaviors continue to be discovered in the worm (*4*, *5*). Although such findings neatly fit in with the connectome, by themselves, connectomes rarely explain or predict network function or behavior. Studies of small, well-understood neural circuits, such as the crustacean stomatogastric ganglion with ~30 neurons, have revealed how molecular and cellular neuronal properties, including the types and modulation of synapses, are essential to understanding network computation (*6*). So how much can be gleaned from connectivity alone?

Compared with studies of a single individual, the comparative connectomics approach enables the extraction of more information about the extent to which connectivity correlates with behavior. Only in nematode worms have whole-animal connectomes been compared across developmental stages (*7*, *8*) and sexes (*9*). Cook *et al.* build on this work by comparing connectomes of related species. The authors chose *P. pacificus*, a nematode that diverged from a common ancestor with *C. elegans* more than 100 million years ago (see the photo). *P. pacificus* has a similar number of neurons as *C. elegans* (*10*); however, in contrast to *C. elegans*, which feeds on bacteria, *P. pacificus* is a predatory animal (that can feed on *C. elegans*) and has an accompanying set of species-specific behaviors (*11*). Previous studies have compared partial connectomes of these two species and identified some changes in wiring and neural correlates of the difference in feeding behavior (*11*, *12*).

On the basis of reconstructions of electron microscopy sections of two adult *P. pacificus* heads, Cook *et al.* report extensive rewiring compared with *C. elegans*. Notably, differences in wiring were distributed throughout the connectomes with no bias for a particular neuron type or brain region. This argues against a particular "circuitry hotspot" of evolutionary change. Species-specific synapses accounted for only 11% or less of all *C. elegans* or *P. pacificus* synapses, but most neurons form at least some species-specific synapses. Hence, despite a clear switch in feeding behavior, the underlying circuitry likely changed at many levels, ranging from the molecular to the circuit level, that contribute together to the behavioral change. Cook *et al.* identified differences in the types and location of neurons, cell death, axon-dendritic growth patterns, and synaptic connectivity between the two species despite the overall morphology of homologous neurons being broadly conserved. To give one example, in *C. elegans*, the Ring/Pharynx (RIP) interneuron receives information from the nerve ring (the main component of the worm's brain) and produces output in the enteric nervous system; in contrast to this strictly unidirectional connectivity, the homologous neuron in *P. pacificus* exhibits a partial polarity change and appears to have synaptic output in both the nerve ring and the enteric nervous systems. This change could affect predatory feeding behavior, but the connectomic evidence alone is not sufficient to demonstrate such a link.

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Not all alterations to the connectome are candidates for behavioral change. For example, the ASH sensory neurons are central to avoidance behavior based on chemical repellents or nose touch and connect to different downstream neurons in *C. elegans* and *P. pacificus*. Yet Cook *et al.* found that ASH-dependent nociceptive responses are indistinguishable between the two species. This is an example of "neural circuit drift," which describes the idea that underlying network topology can change (drift) while behavioral output remains constant. Identifying connectomic changes that do and do not alter behavior may thus provide clues about which synaptic connections and connectivity patterns underlying a specific behavioral output are essential and which are flexible. Looking at essential connections, together with artificial intelligence–augmented methods, has recently yielded some success in predicting network computation based on the fly connectome (*13*). It is not clear to what degree such an approach could help decipher the behavioral switch from bacteria to predatory feeding in the worms, but the findings of Cook *et al.* suggest that the change in behavior is not based on a simple change of one or a few synaptic connections. Instead, understanding causal feedback between molecular, cellular, and network changes is likely to be critical.

The findings of Cook *et al.* should be viewed within the context of nematode evolution and development. Evolutionary selection caused dramatic genomic changes during the 100 million years that separate *C. elegans* and *P. pacificus* from their presumptive common ancestor: The *P. pacificus* genome is 70% larger than that of *C. elegans* and contains 30% more protein-coding genes (*14*). However, genomes contain information that enables the growth of the connectome, not information that describes the outcome. Therefore, to understand how these genomic changes affect synaptic connections requires the identification of the relevant developmental processes. For example, the two species exhibit substantial differences in the timing of postembryonic developmental stages (heterochrony). An analysis of gene expression during development had previously revealed that thousands of gene transcripts exhibit oscillations in their levels, many of which differ substantially between the two worm species (*15*). This indicates that, just as the change in feeding behavior is not based on a change in one or a few synaptic connections, the connectivity changes do not arise from a change in one or a few genes.

Although how heterochrony is genetically controlled remains unclear, it will likely affect how long specific pairs of neurons have to form synapses with each other. Throughout development, some subsets of neurons spend more time in close proximity than others. Spending more time near each other may increase the likelihood of forming a connection. Such neuronal adjacencies, also described as the "contactome," were recently found to largely predict synaptic connectivity in the *C. elegans* connectome (*8*). Cook *et al.* found that connectivity differences between the two worm species correlated well, but not perfectly, with adjacencies. However, the absence of developmental connectomes for *P. pacificus* represents a limitation of their analysis. Overall, the extent to which developmental adjacencies are sufficient to predict the adult connectome remains to be determined.

A consequential lesson learned from Cook *et al.*'s cross-species comparison of two whole-animal connectomes, then, is that a dramatic switch in (feeding) behavior is not based on a simple change to a single synaptic connection or connectivity pattern. This lesson may prove important for the design of future experiments aimed at understanding the causal relationships between the connectome and behavior, even if it does not make them easier. The findings from comparative studies of compact, relatively simple nervous systems, such as those of worms and flies, suggest that the power of connectomics does not only come from the generation of large-scale connectomes. If circuit alterations underlying behavioral change are formidable in small, tractable circuits, so, too, may be the principles to be learned from them. □

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