cells. UGDH converts UDP-glucose (UDP-Glc) to UDP-glucuronic acid (UDP-GlcUA), which is needed to make polysaccharide molecules such as hyaluronic acid, a component of the extracellular matrix material in the tissues in which epithelial cells reside. Hyaluronic acid can activate receptors on the surface of cells to initiate EMT, and its accumulation in tumours is often associated with poor clinical outcome[5].

Surprisingly, when the authors inhibited UGDH expression, cell migration was not impaired as a result of reduced levels of UDP-GlcUA or hyaluronic acid, but because of an accumulation of UDP-Glc. Because EMT in cancer cells is associated with an increase in their migration[1], the authors investigated whether UDP-Glc has an effect on the induction of EMT. They found that depletion of UGDH, and hence UDP-Glc accumulation, was accompanied by a decrease in the stability of messenger RNA that encodes a transcription-factor protein called SNAIL. This transcription factor regulates the expression of genes associated with EMT[1]. When the authors engineered cancer cells so that SNAIL was produced, the cells migrated even when UGDH was depleted. These results indicate that UGDH acts in a pathway that regulates cell migration by affecting SNAIL production (Fig. 1).

How might a metabolic enzyme such as UGDH affect mRNA stability? The authors focused on HuR, a protein that binds to and stabilizes mRNA targets[6], including the transcript that encodes SNAIL. They found that UDP-Glc binds directly to HuR, thereby preventing the protein from interacting with the mRNA that encodes SNAIL. The authors engineered a form of HuR that had mutations in the amino-acid residues predicted to coordinate its binding to UDP-Glc. Compared with cells that had wild-type HuR, those with the mutant form were found to be more likely both to form metastases in mice and to migrate *in vitro* across a membrane in a culture dish.

This suggests that an interaction between UDP-Glc and HuR prevents HuR from acting in a pathway to induce cellular programs that promote metastasis. When the authors injected tumour cells into mice and gave UDP-Glc to some of them, those that received UDP-Glc had fewer metastases than the animals that did not receive it.

There are intriguing hints that the authors' findings might have relevance for human cancer. In lung cancer, the receptor EGFR is commonly activated by mutations[7], and the authors found that an increase in signalling through this receptor is associated with increased stability of SNAIL-encoding mRNA in human lung cancer cells grown *in vitro*. They observed that EGFR activation triggers the phosphorylation (the addition of a phosphate group) of the amino-acid residue tyrosine 473 (Y473) in UGDH, inducing a physical interaction between HuR and UGDH.

Wang and colleagues speculate that phosphorylated UGDH bound to HuR causes the local conversion of UDP-Glc to UDP-GlcUA, thereby alleviating UDP-Glc's inhibition of the interaction between HuR and SNAIL-encoding mRNA and promoting SNAIL accumulation (Fig. 1). The authors engineered human lung cancer cells to express UGDH lacking a tyrosine residue at position 473, and found that such cells formed fewer metastases in mice than did cells that had wild-type UGDH. Wang *et al.* also noted that, in people with lung cancer, phosphorylation of Y473 in UGDH was more common in metastases than in primary tumours, and that this phosphorylation was associated with a poor clinical prognosis.

The authors' findings add to growing evidence that metabolites can affect gene-expression programs[8]. The best-known examples of this are cases in which metabolites provide substrates for enzymes that regulate gene expression by modifying chemical groups attached to DNA or to the histone proteins that bind to DNA. However, UDP-Glc instead affects gene expression by physically preventing the interaction between a protein and mRNA. How UDP-Glc specifically affects HuR's interaction with SNAIL-encoding mRNA, without impairing its interaction with other mRNAs, is an open question. Given the links between SNAIL expression, EMT and the extracellular matrix, it is tempting to speculate that coupling the production of SNAIL to the metabolites that generate hyaluronic acid might be an efficient way to coordinate the changes in both metabolism and protein production that are needed to promote metastasis.

Thus, in contrast to the metabolites that accumulate through cancer-associated mutations in metabolic enzymes and promote tumour progression[8], UDP-Glc limits progression. This discovery widens our horizons regarding the ways in which metabolites can influence cancer. Although it has long been recognized that the metabolic profiles of cancer cells differ from those of normal cells, we are only beginning to appreciate the complexity of the metabolic alterations involved in tumour growth. ■

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NEUROSCIENCE

The minds of two worms

Understanding how the brain's functions emerge from the workings of neural circuits is a central pursuit of neuroscience. New wiring diagrams of the nervous system in both sexes of a worm mark important progress. SEE ARTICLE P.63

DOUGLAS S. PORTMAN

Across biology, function follows form. The structure of a wing provides insight into flight; the anatomy of the lung suggests mechanisms for gas exchange. When applied to the brain, however, this approach falters. The uniform, gelatinous consistency of the mammalian brain belies an almost inconceivable cellular complexity: billions of nerve cells (neurons), interacting through trillions of connections (synapses), form circuits that perceive stimuli, store memories and generate emotions. What if we had a complete map of these connections? Would this help us to understand how the brain works? This is the premise of 'connectomics', the systematic identification of all connections in a nervous system. On page 63, Cook *et al.*[1] report the complete connectomes of both sexes of a tiny roundworm — a major step towards understanding how a brain's function emerges from its form.

Long before the word connectomics was first uttered, the ideas behind it were apparent to the late Sydney Brenner, who, in the 1960s, famously sought to 'tame' a creature whose nervous system might be completely mapped[2]. Brenner settled on the millimetre-long nematode *Caenorhabditis elegans*, affectionately known to those who study it as 'the worm'. The worm's nervous system comprises just a few hundred neurons, whose position and overall structure are identical between individuals.

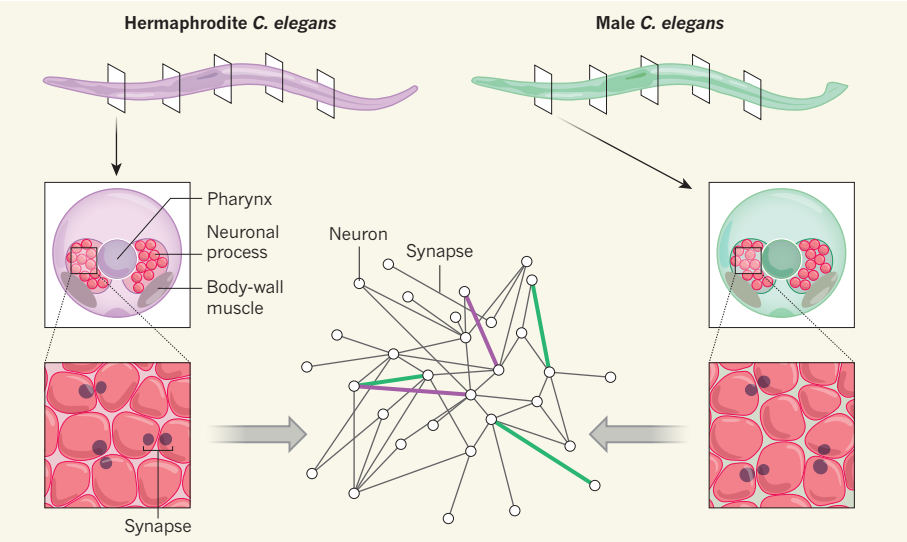

Figure 1 | Mapping the mind of the worm. Cook *et al.*[1] have mapped, at subcellular resolution, the complete nervous systems of both sexes (hermaphrodite and male) of the nematode worm *Caenorhabditis elegans*. Top, the investigators used tens of thousands of serial sections covering most of the body of the adult worm. Low- and high-resolution microscopy images were taken of these sections, revealing the anatomy of a typical section, including the neuronal processes and synaptic connections. The authors used these images to construct a connectome — a map showing the connections between all the neurons, a simplified version of which is depicted here (centre). Most connections are present in both sexes (grey), but some are present only in one sex, or are stronger in one than in the other (purple and green).

Yet it controls complex, instinctive behaviours, allows these to be modified according to a worm's needs, and learns simple associations.

The worm is small enough to imagine slicing it up like a tiny salami, and, with tremendous patience, tracing the structure of each neuron and its connections across microscopy images of the slices (Fig. 1). Exactly this was heroically undertaken in the 1970s and 1980s. The resulting connectome — the first of its kind — was reported in a classic 1986 paper[3] known colloquially as 'The mind of the worm'. Important refinements have followed[4–6], and neurobiologists have been working diligently to understand how behaviour emerges from the circuits described.

But this connectome was for only one sex, the hermaphrodite — a self-fertile individual that is considered the worm's female equivalent. So the extent of sex differences in the wiring has been unclear. Moreover, because the original connectome was built manually, it remained possible that it contained some errors. To address these problems, workers from the same group as Cook *et al.* developed and used software[7] to reconstruct the connectome of the adult male's tail, a region that houses circuits present only in this sex. Now, Cook *et al.* report the rest of the male connectome, including the nerve ring — the region in the head in which the worm's heavy computing takes place. Not satisfied with this, the authors also rebuilt the entire hermaphrodite connectome from scratch, using their software to reanalyse the original 1980s micrographs.

These new connectomes reveal rich, nuanced information that will advance the field in many ways. Whereas the original connectomes report each synapse as simply being present, Cook *et al.* provide each with a physical location and a weight — an indirect measure of strength based on physical size. This level of detail will enable much more sophisticated analysis and modelling of circuit function. Thanks to the software's sensitivity, the researchers also identify thousands of previously overlooked connections in the hermaphrodite. Using the tools of network theory, they provide interesting new classifications of groups of neurons on the basis of their connectivity. By comparing their reconstructions of the worm's left and right sides, which are largely symmetrical, the authors estimate the accuracy of their connectome data, which is reassuringly high.

The new connectomes also include the outputs of the nervous system — features that have never been catalogued rigorously in any organism. This reveals previously unknown connections to the intestine, epidermis and male gonad that will surely inspire new ideas about worm physiology and metabolism. The authors also find unexpected complexity in the control of body muscles; this might force neuroscientists to reconsider their understanding of how movement emerges from circuit function.

And what about sex differences? Remarkably, Cook *et al.* find that numerous connections — up to 30% — seem to differ in strength between hermaphrodites and males. Differences such as these have already been noted in the tail, where they optimize copulatory behaviour[7,8]. But their preponderance in the head, where the gross anatomy of the nervous system is nearly equivalent between the sexes, is surprising.

The authors confirmed some of these differences by directly visualizing particular synapses in live worms. This showed that the average size of certain connections does indeed differ by sex, but also that ranges of size can overlap substantially. Thus, as in other systems, biological sex can nudge developmental mechanisms, creating tendencies as well as absolute differences. The sex differences identified do not radically change the structure of the connectome, but they do raise fascinating questions about how these alterations modulate decision-making and behaviour.

The study does have some limitations. Because most regions were reconstructed just once, the amount of variation between individuals remains unknown. Some features of the new connectomes could arise from past experiences specific to the individuals that were sampled. Another issue regards the synaptic weights: it's not clear how a connection's strength might scale with its physical size. Finally, although the connectomes include many new connections, they also lack some that were present in the previous versions. So, can we consider the new connectomes 'complete'? This is as much a philosophical issue as a technical one.

The new connectomes highlight a vexing point about neural circuits and the promise of connectomics itself: inferring function from structure alone is fraught with difficulty. Depicted graphically, the new connectomes don't obviously resemble artificial neural networks or the wiring schematics of simple electronic devices; they look more like the cobwebs that lurk at the back of the broom cupboard. Most neurons are extensively interconnected with many others, such that any two are linked through a very short path. Although intriguing patterns can be identified, distinct circuits for specific behavioural responses are not readily apparent. As others have pointed out[9], the connectome is only a map of possibilities. Functional circuits probably emerge spontaneously through the dynamic modulation of individual synapses. The connectome shows all these synapses simultaneously, offering few clues about which might be active at a given time.

Thus, the physical structure of the connectome provides essential insight into the nervous system, but is in itself insufficient for an understanding of the whole. Fortunately, groundbreaking imaging approaches could bridge the chasm between circuit structure and function. Using fluorescent indicators of neuronal activity, it is now feasible to 'watch' signals flow through the nervous system of a freely behaving worm in real time[10,11]. Superimposing these activity patterns onto the connectome should provide the information necessary to understand how the nervous system's structure constrains its function. This, in turn, will bring us closer to building a detailed simulation of the nervous system, generating a virtual worm that 'lives' inside a computer[12].

This is still far off; but only if we can accurately simulate and rationally manipulate a nervous system can we begin to truly understand it. Once again, Brenner's tiny worm, occupying its unique sweet spot between simplicity and complexity, finds itself on the front line of biology's most challenging problems. ■

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COMPUTATIONAL MATERIALS SCIENCE

Text mining facilitates materials discovery

Computer algorithms can be used to analyse text to find semantic relationships between words without human input. This method has now been adopted to identify unreported properties of materials in scientific papers. SEE LETTER P.95

OLEXANDR ISAYEV

The total number of materials that can potentially be made — sometimes referred to as materials space — is vast, because there are countless combinations of components and structures from which materials can be fabricated. The accumulation of experimental data that represent pockets of this space has created a foundation for the emerging field of materials informatics, which integrates high-throughput experiments, computations and data-driven methods into a tight feedback loop that enables rational materials design. On page 95, Tshitoyan *et al.*[1] report that knowledge of materials science 'hidden' in the text of published papers can be mined effectively by computers without any guidance from humans.

The discovery of materials that have a particular set of properties has always been a serendipitous process requiring extensive experimentation — a combination of craft and science practised by knowledgeable artisans. However, this trial-and-error approach is expensive and inefficient. There is therefore great interest in using machine learning to make materials discovery more efficient.

Currently, most machine-learning applications aim to find an empirical function that maps input data (for example, parameters that define a material's composition) to a known output (such as measured physical or electronic properties). The empirical function can then be used to predict the property of interest for new input data. This approach is said to be supervised, because the process of learning from the training data is akin to a teacher supervising students by selecting the subjects and facts needed for a particular lesson. A contrasting approach involves using only input data, which have no obvious connection to a specific output. In this case, the goal is to identify intrinsic patterns in the data, which are then used to classify those data. Such an approach is called unsupervised learning, because there are no a priori correct answers and there is no teacher.

Tshitoyan and colleagues collected 3.3 million abstracts from papers published in the fields of materials science, physics and chemistry between 1922 and 2018. These abstracts were processed and curated, for example to remove text that wasn't in English and to exclude abstracts that had unsuitable metadata types, such as 'Erratum' or 'Memorial'. This left 1.5 million abstracts, which were written using a vocabulary of about 500,000 words.

The authors then analysed the curated text using an unsupervised machine-learning algorithm known as Word2vec (ref. 2), which was developed to enable computers to process text and natural language. Word2vec takes a large body of text and passes it through an artificial neural network (a type of machine-learning algorithm) to map each word in the vocabulary to a numeric vector, each of which typically has several hundred dimensions. The resulting word vectors are called embeddings, and are used to position each word, represented as a data point, in a multidimensional space that represents the vocabulary. Words that share common meanings form clusters within that space. Word2vec can therefore make accurate estimates about the meaning of words, or about the functional relationships between

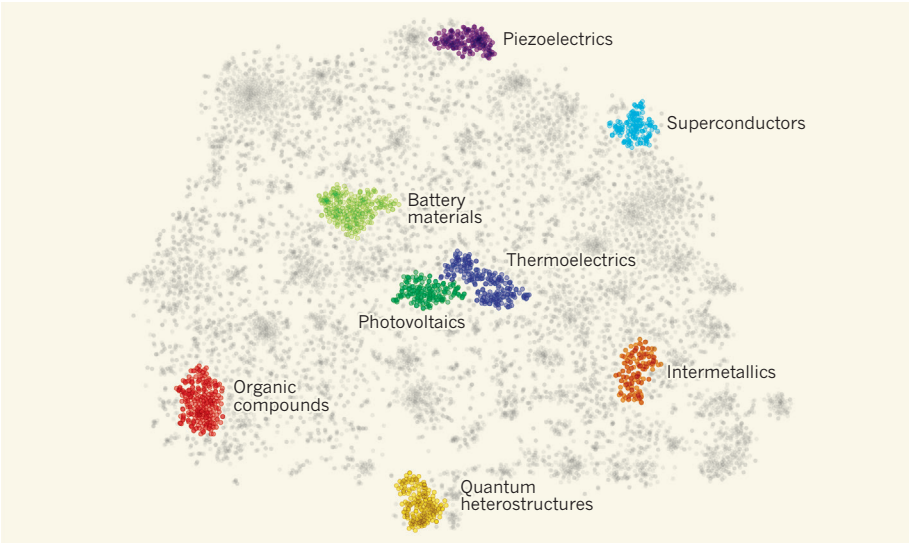

Figure 1 | Clustering of materials from textual analysis of scientific papers. Tshitoyan *et al.*[1] used a machine-learning algorithm to analyse the text in the abstracts of 1.5 million papers to identify relationships between words, including the names of materials. Individual materials were then represented as data points on graphs, and the algorithm clustered the data points together on the basis of the semantic relationships between the words used to describe those compounds. The clusters (coloured) correspond to particular types of material, such as superconductors, battery materials and organic compounds. The authors show that this approach can be used to identify unreported properties of materials mentioned in the scientific literature. (Adapted from Fig. S7a of the paper[1].)