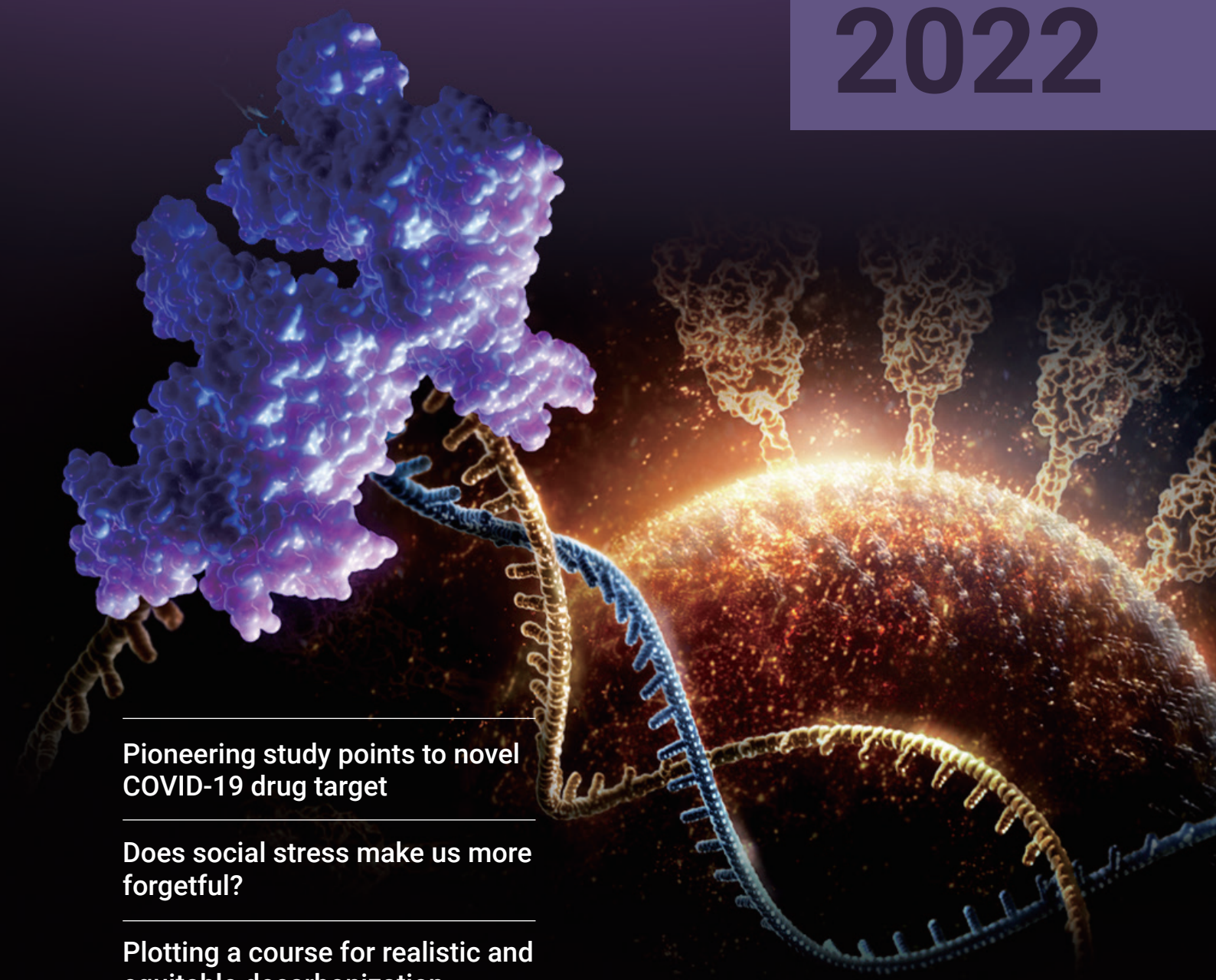
RESEARCH FEATURE 2022



Pioneering study points to novel COVID-19 drug target

Does social stress make us more forgetful?

Plotting a course for realistic and equitable decarbonization

Mental-health support chatbots

清華大學
Tsinghua University

FOREWORD

Tsinghua scientists and researchers have continued expanding the frontiers of science and technology through innovative thinking, interdisciplinary approaches, and groundbreaking research. Their research projects have focused on topics ranging from some of the most pressing problems of our times, such as Covid-19 and climate change, to future technologies.

Researchers led by Zihe Rao and Zhiyong Lou of Tsinghua used a cryo-electron microscope to image the complex of proteins that comes together inside infected cells of COVID-19 patients, enabling the virus to transcribe RNA copies of the virus gene sequence and replicate. What they have discovered may offer insights into thwarting the virus.

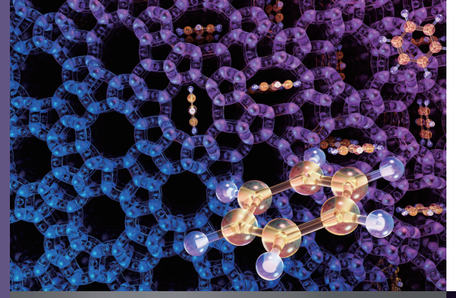
In yet another study, a Tsinghua team developed a self-taught deep learning system that can detect four different conditions – stroke, brain haemorrhage, brain tumors and skull fractures. Their artificial intelligence (AI) performed at 96% accuracy, the same rate as radiologists. Their AI system might make the diagnostic process as fast and effective as possible.

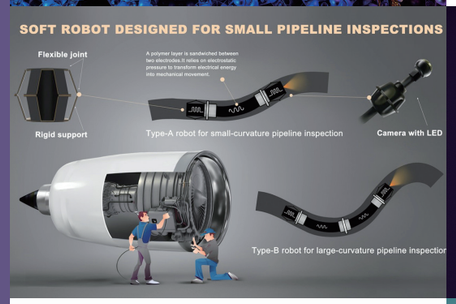
Earlier this year, Huichan Zhao, a mechanical engineer at Tsinghua University, and her collaborators published the details of a soft robot designed to mimic the movement of earthworms, which could be used to perhaps inspect the narrow pipes found in machinery such as aircraft engines. One day, she hopes her earthworm-inspired robot could replace the fibre-optic cables typically used to inspect these pipes today.

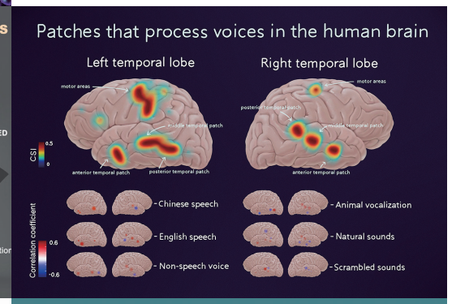
In a paper published last December in the Proceedings of the National Academy of Sciences, Xiaoqin Wang, a professor of biomedical engineering at Tsinghua University and the head of Tsinghua Laboratory of Brain and Intelligence, and his collaborators found specialized regions within the brain that are responsible for processing the voices we hear, offering new knowledge on how we speak, how we hear, and how we interact with others across a lifetime.

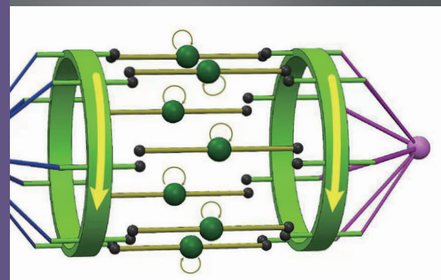
A new study, done by Tsinghua's School of Life Sciences, focused on how social stress or reward might affect the brain's internal filing system. Its findings showed that negative or positive social environments stimulate a protein that temporarily makes some memories harder or easier to access, suggesting that social stress causes a disruption in recent memories and makes some memories harder or easier to access.

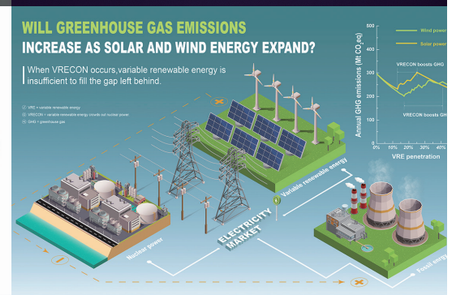
The Research Feature 2022 offers a closer look at some of these research accomplishments while providing insights into the world-class research environment Tsinghua offers to make innovation happen.

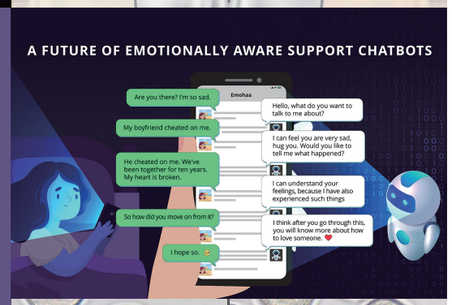


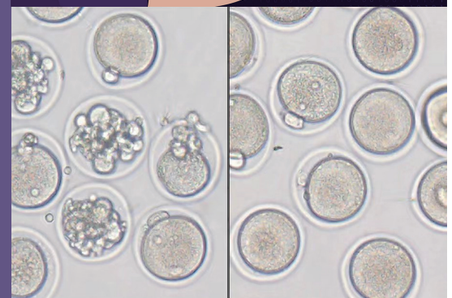












CONTENTS

RESEARCH FEATURE

Electronic rotating ‘neurons’ offer brain-like computing

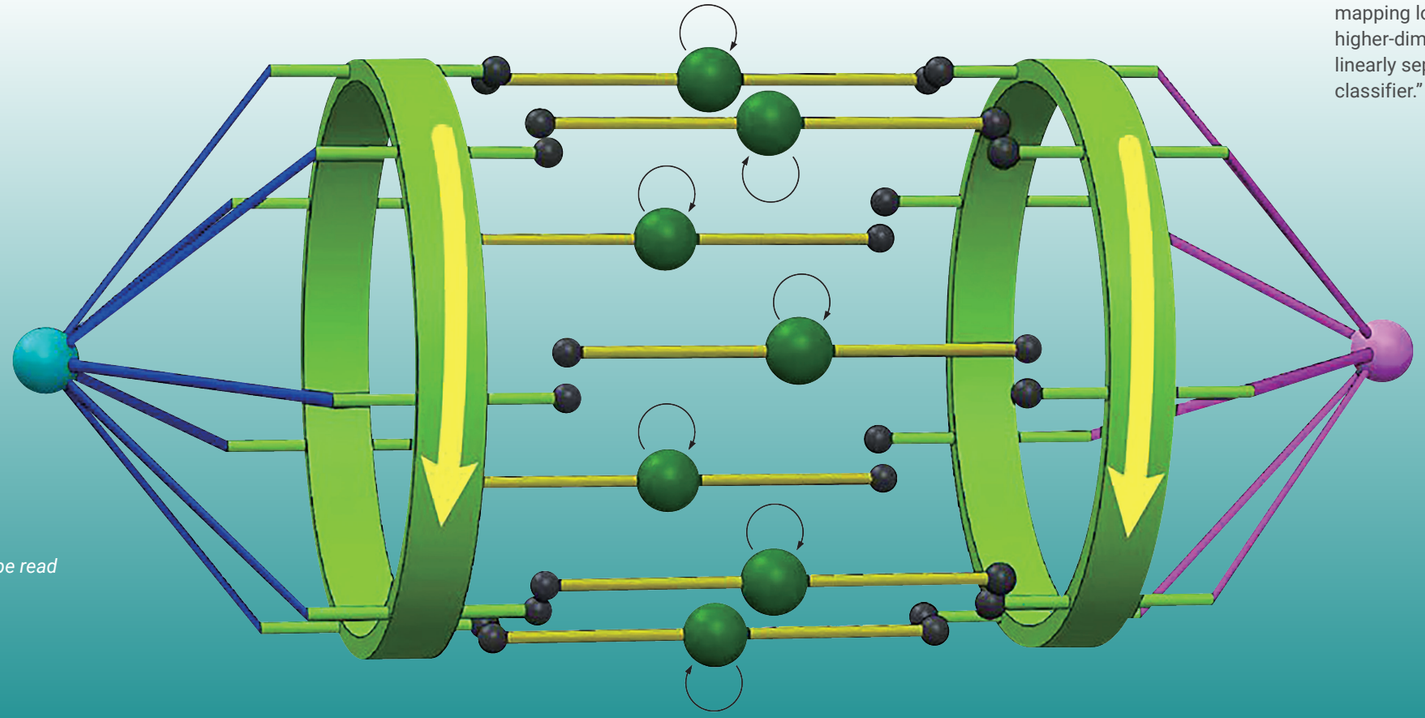
A prototype computer that mimics the analog physical computational dynamics of the brain could lead to more efficient and more powerful problem-solving platforms.

Using off-the-shelf electronic components, a Tsinghua University-led research team has built a complete prototype ‘reservoir’ computer as a low-power, high-speed alternative to today’s binary-based computer systems. The research, published in *Nature Communications*[1], demonstrates the potential of analog-based brain-mimicking hardware architecture for solving complex problems and efficiently training neural networks.

The promise of reservoir computing

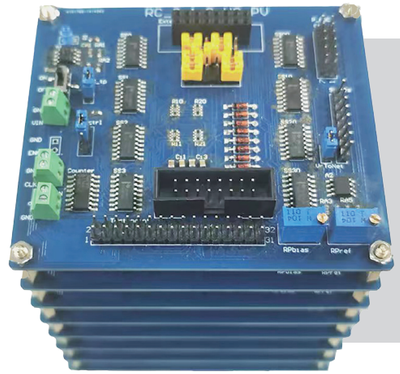
Today’s computers are based on the processing of binary data – 0s and 1s – through complex logic networks. The brain, however, offers an enticingly different and promising computing principle. It operates on many different inputs at once, with each neuron connected to many others in a time-varying cascading network – a highly efficient biological computer that operates not on 1s and 0s, but in a non-linear analog domain. Mathematically, this could be modelled as a ‘reservoir’ computer, as He Qian from the Beijing National Research Center for Information Science and Technology (BNRist) at Tsinghua University, explains.

“Reservoir computing is a form of neuromorphic computing that was first proposed in the 2000s,” says Qian. “It can be most easily understood using a lake analogy. If you throw stones into a lake, the ripples from each stone interact to produce a complex ripple pattern on the water surface as a fading memory containing the information about your stone-throwing activity. By analysing the ripples, it is possible to understand how many stones you threw, the time intervals between them, and even how big each stone was. The lake is a ‘reservoir’, and the ripple pattern is the reservoir’s state matrix. Similar processes, including high-dimensional mapping and readout, have been recently found in the mouse brain, which suggests our brain might operate as a complex reservoir computing system as well.”



Rotating neurons (green) provide a cyclic reservoir that processes inputs (blue) to be read out as linearly classified outputs (pink).

Since the idea was proposed, researchers have been studying different ways to implement such a computing system in hardware, but so far such experiments have required elaborate input and readout systems. Qian and Huaqiang Wu from BNRist with a group of colleagues have now designed, simulated and constructed an electronics-based reservoir computing system with integrated input and readout capability that demonstrates the promise of this approach for powerful, very low energy computing.



Electronic implementation of a rotating neuron reservoir as a stack of eight 8-neuron circuits.

A benchtop brain

Using a stack of electronic circuits including a readout module consisting of an array of memristors — resistive switching elements that ‘remember’ the amount of charge that has flowed through them — the team constructed a circuit modelling a reservoir of rotating neurons that respond to inputs in a sequential and interconnected way.

“Our main challenge was to find an equivalent pairing of a neural network algorithm and hardware that could be implemented,” says Qian. “In this case, the electronic rotational hardware has a similar function to the ‘lake’ reservoir, mapping low-dimensional inputs to a higher-dimensional space that can be linearly separated using a simple linear classifier.”

The team’s device achieves all-analog signal processing with extremely low power, three orders of magnitude lower than any other reservoir computing system, and was used to accurately predict the future sequence of a chaotic time series as a potential sensor application.

“There is more to electronics than the binary transistor,” Qian says. “There remains much to be explored in the rich dynamics offered by electronics for neuromorphic reservoir computing, which is particularly interesting for brain-inspired computing and artificial intelligence due to its low training complexity and cost.”

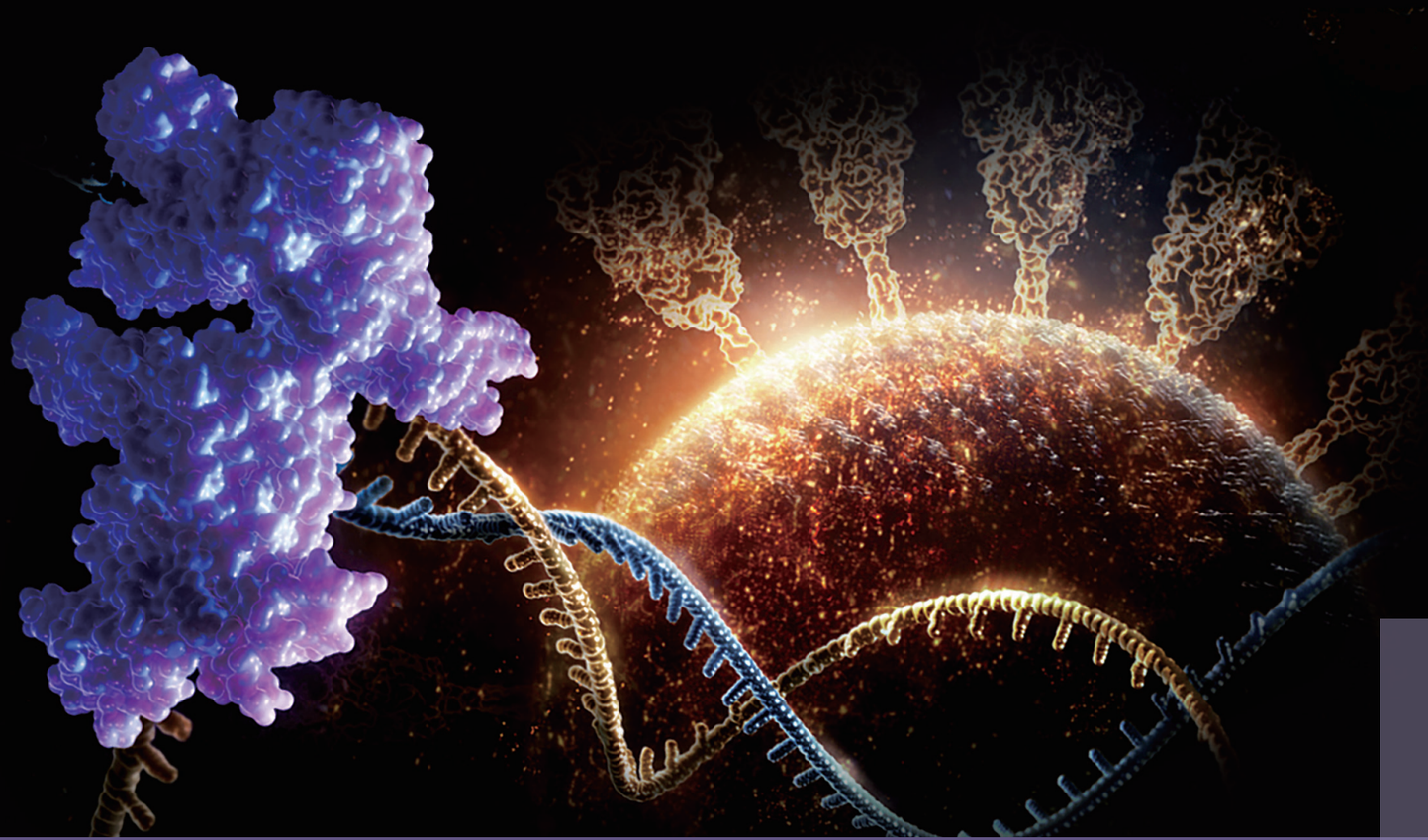
Reference

[1] Liang, X. *et al*. Rotating neurons for all-analog implementation of cyclic reservoir computing. *Nature Communications* **13**:1549 (2022). Engineering 32, 408-415 (2021). https://doi.org/10.1016/j.cjche.2020.11.023

RESEARCH FEATURE

Pioneering study points to novel COVID-19 drug target

Insights into the transcription and replication mechanisms of SARS-CoV-2 offer a new way to fight it.



Tsinghua researchers have revealed key structures of the Replication-Transcription Complex that are essential to the SARS-CoV-2 lifecycle.

New insights into viral replication and transcription, led by researchers at Tsinghua University[1,2], may help pinpoint fresh targets for drugs and vaccines against emerging SARS-CoV-2 variants.

Researchers led by Zihe Rao and Zhiyong Lou have used a cryo-electron microscope to image the complex of proteins that comes together inside infected cells of COVID-19 patients, enabling the virus to transcribe RNA copies of the virus gene sequence and replicate. What they have discovered may offer insights into thwarting the virus.

The pandemic has been prolonged by the emergence of many new SARS-CoV-2 variants, often with mutations in the 'spike' protein the virus uses to enter cells. As many COVID-19 vaccines are targeted at the spike protein, these mutations have helped some variants evade the immunity conferred by vaccines.

Much less prone to mutation, however, is the Replication-Transcription Complex – the set of viral proteins that come together during replication to allow SARS-CoV-2 to proliferate.

"The catalytic residues of Replication-Transcription Complex proteins are almost identical, or at least very similar, among different SARS-CoV-2 variants," says Lou. "Which suggests the potential to develop broad-spectrum antiviral drugs that target the replication process."

RNA cap of SARS-CoV-2

Tsinghua researchers have a long track record of studying the internal mechanisms of coronaviruses. Co-leader of the study, Zihe Rao, has worked in the field since the emergence of SARS-CoV (the virus that causes the disease SARS) in 2003. "SARS-CoV-2 shares high similarity with SARS-CoV," says Lou, meaning they could bring their expertise to bear on studying the newly-emerged virus.

One key feature of SARS-CoV-2 RNAs, as synthesized by the Replication-Transcription Complex during replication, is a protective 'cap' affixed to one end of the RNA strand. "This structure is important to the stability of viral RNA and can help it escape the host's innate immune response," says Lou.

The complex constructs the cap in a four-step process. The role of the protein that catalyzes the second step of the capping process, called nucleotidyl transferase domain (NiRAN), was a mystery until this study[1]. "We showed that the NiRAN domain in the replication enzyme, viral polymerase nsp12, is indeed the enzyme that catalyzes the second capping action," Lou explains.

In a subsequent study, the group also revealed the mechanism underlying the third capping action and the

Liming Yan (centre) and his colleagues analyze cryo-electron microscope data on an enzyme that catalyzes key steps in SARS-CoV-2 replication.

proofreading process (to ensure the SARS-CoV-2 sequence is accurate) are found in the Replication-Transcription Complex[2].

Assembling a Replication-Transcription Complex in the lab, in order to take the cryo-electron microscope image with the molecule in position, was a great challenge, Lou says. "We had to test many different conditions to catch these temporary complexes," he says.

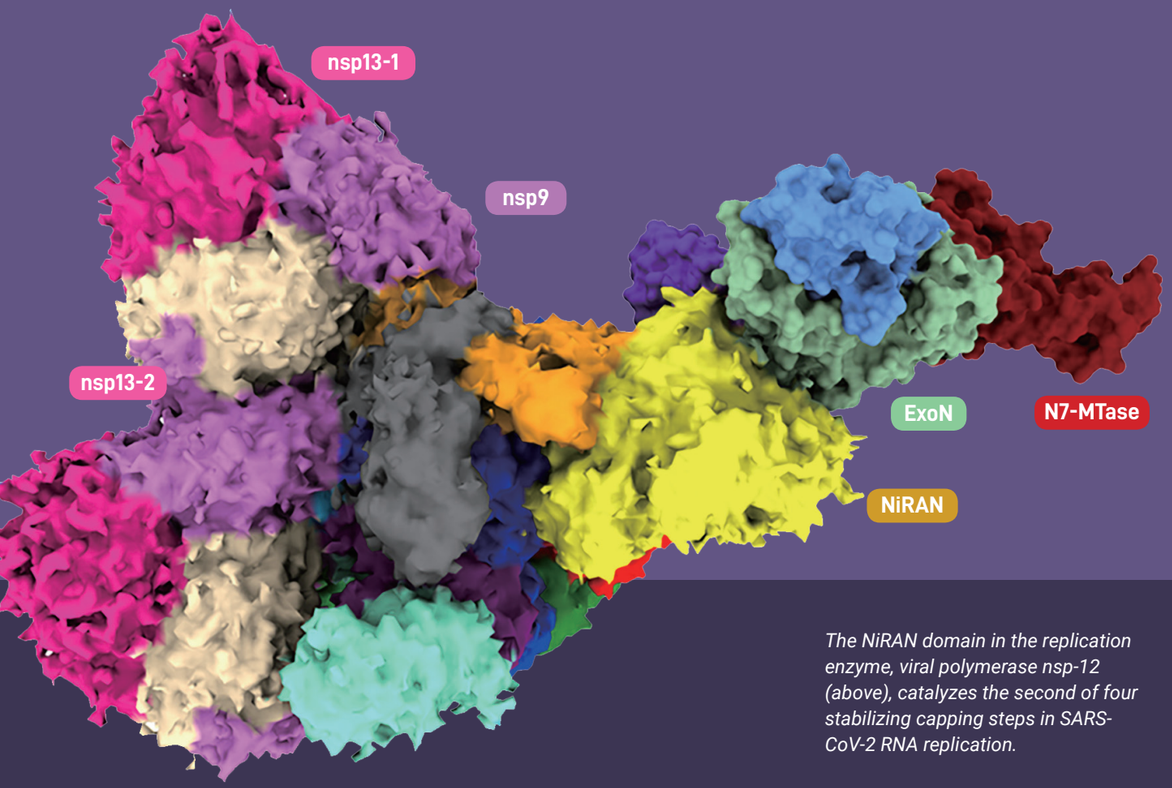
"These studies were highly dependent on the close coordination of more than 10 researchers," says Lou. For example, for one cryo-electron microscope data set, his team worked intensively for more than three days and nights to simultaneously freshly prepare the proteins required.

Understanding that the nsp12-NiRAN region plays a key role in stable virus RNA cap formation offers new, highly stable targets for researchers seeking drugs to inhibit SARS-CoV-2 replication. Importantly, they are also expected to work against new variants. "We are now collaborating with researchers, including medicinal chemists, and hope to identify leading compounds for drug development soon," says Lou.

References

[1] Yan, L., Ge, J., Zheng, L., Zhang, Y., Gao, Y., *et al*. Cryo-EM Structure of an Extended SARS-CoV-2 Replication and Transcription Complex Reveals an Intermediate State in Cap Synthesis. *Cell* **184**, 184–193 (2021) doi: 10.1016/j.cell.2020.11.016

[2] Yan, L., Yang., Y, Li, M., Zhang, Y., Zheng, L. *et al* Coupling of N7-methyltransferase and 3'-5' exoribonuclease with SARS-CoV-2 polymerase reveals mechanisms for capping and proofreading. *Cell* **184 (13)**, 3474-3485 (2021) doi: 10.1016/j.cell.2021.05.033



The NiRAN domain in the replication enzyme, viral polymerase nsp-12 (above), catalyzes the second of four stabilizing capping steps in SARS-CoV-2 RNA replication.

Boosting carbon capture potential at power stations

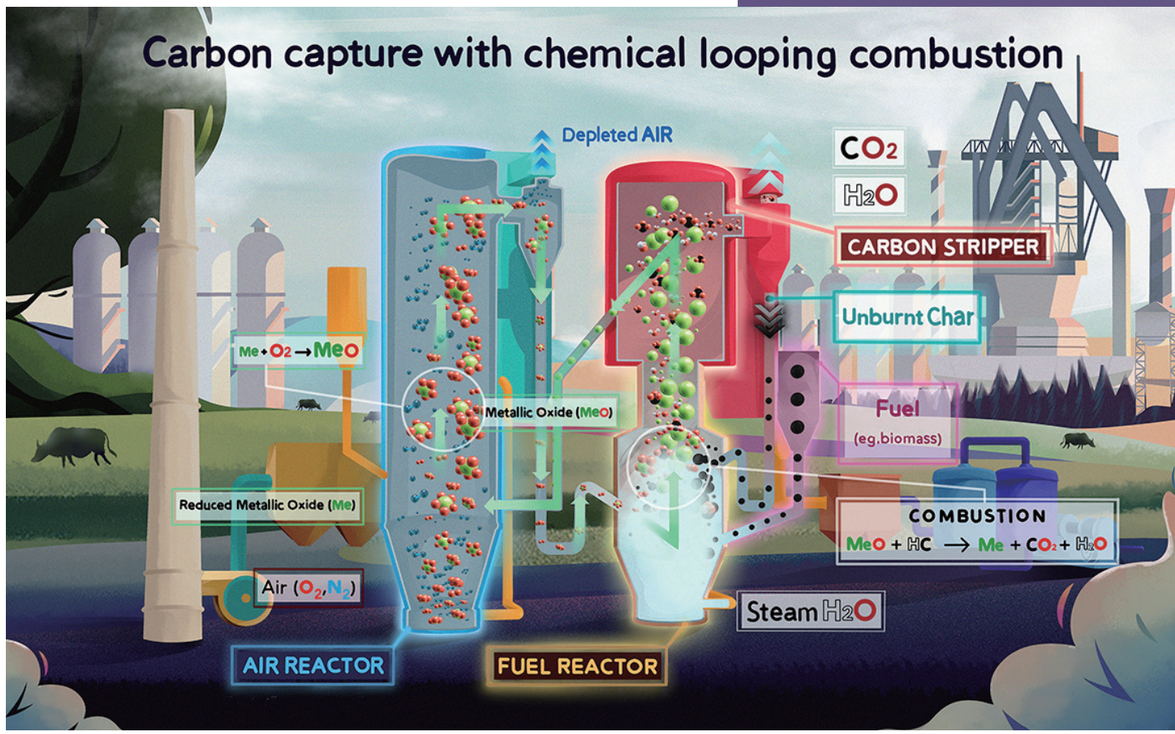
Now that oxygen carrier materials can be manufactured at an industrial scale, chemical looping combustion technology could help generate clean heat and electricity with near zero emissions.

Technology for capturing carbon dioxide and storing it permanently underground is expected to be vital in strategies to restrict global temperature rises, according to an April 2022 report released by the United Nations Intergovernmental Panel on Climate Change. Chemical looping combustion (CLC) is recognized as one of the most innovative CO_2 capture technologies because of low energy penality. An important step in this direction is a new industrial means of producing an affordable solid metal oxide[1] – a perovskite oxygen carrier material developed by a Tsinghua team in 2021[2].

Efficient production of the oxygen carrier should enable the power generation industry to incorporate an emerging, highly efficient carbon capture technology into its combustion processes, explains Zhenshan Li, who leads the Tsinghua team.

Chemical looping combustion technology is more efficient than existing carbon capture technologies, he says. The flameless combustion approach has just two end products: steam and carbon dioxide. The former

Zhenshan Li's team have developed an affordable way to produce an efficient metal oxide-based oxygen carrier . This advance, he says, should enable chemical looping combustion to be incorporated into power generation systems, significantly reducing the amount of CO_2 emitted.



A perovskite oxygen carrier material developed by a Tsinghua team in 2021, after calcination.

can be used to run steam turbines, while, unlike other technologies, the carbon dioxide produced by CLC is pure enough to be sequestered immediately without the need for further expensive and energy-intensive processing.

CLC relies on adding solid oxygen carriers, rather than oxygen gas, during the combustion process, explains Li. "The solid oxygen carrier is then able to more efficiently generate gaseous oxygen in the fuel reactor environment," he says.

A workable oxygen carrier

The identification of a suitable oxygen carrier had been holding back attempts to scale-up CLC technology. Most researchers have focused on using perovskite oxides containing precious and transition metals. These are too expensive for this purpose, says Li. "The oxygen carrier material must be cheap and environmentally friendly," he says.

In 2021, Li's team at Tsinghua's Department of Energy and Power Engineering published in the *Chinese Journal of Chemical Engineering* on an inexpensive perovskite oxide ($CaMn_{0.5}Ti_{0.375}Fe_{0.125}O_{3-\delta}$) with excellent oxygen transfer capacity and stability[2]. Now, the same team has revealed, in the *Chemical Engineering Journal*, a route to manufacture this perovskite oxide at volumes suitable for industrial use of CLC[1].

The new production protocol is an adaptation of a well-known particle production method – spray drying – where a liquid slurry is atomized into droplets before being flashed dried to form solid particles. "The traditional spray drying method produces particles that are < 100 μm, but chemical looping requires an oxygen carrier particle size of 100 to 300μm," explains Li. Several changes were made to increase the size of particle produced, including pressurizing the liquid slurry before spraying and adjusting the drying temperature.

Using their new protocol, Li and his team can continuously manufacture the perovskite oxide at a rate of roughly 2500 kg/h. The researchers also tested their new particles under conditions that closely mimic those of a CLC system, finding that their physical and chemical properties were the same as those produced previously by large particles produced in small batches in laboratories.

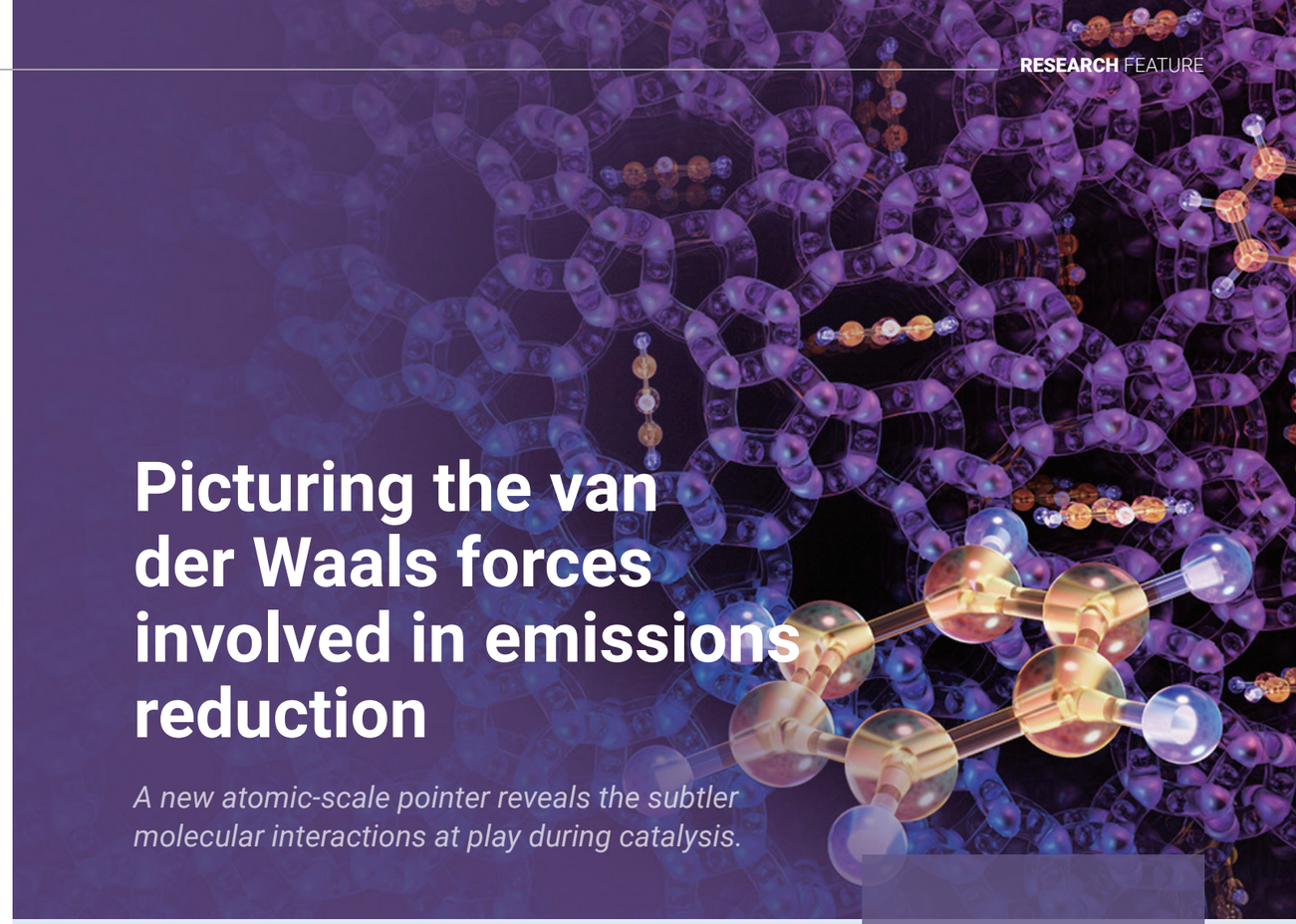
CLC has not yet been implemented at an industrial site, but pilot plants are starting to emerge, says Li. These include a 30 kW pilot unit at Tsinghua University, a 100 kW unit and the world's largest 5 MW demonstration unit in the city of Deyang in southern China, all designed by his team.

Pressurizing a perovskite oxide liquid slurry and adjusting the spray-drying temperature in the above device produced particles at a useful size.

References

[1] Liu, L., Zhenshan, L., Wang, Y., Li, Z., Larring, Y. *et al*. Industry-scale production of a perovskite oxide as oxygen carrier material in chemical looping. *Chemical Engineering Journal* **431**, 134006 (2022). https://doi.org/10.1016/j.cej.2021.134006

[2] Liu, L., Zhenshan, Li., Yi, L. & Cai, N. Evaluation of oxygen uncoupling characteristics of oxygen carrier using micro-fluidized bed thermogravimetric analysis. *Chinese Journal of Chemical Engineering* **32**, 408-415 (2021). https://doi.org/10.1016/j.cjche.2020.11.023



Picturing the van der Waals forces involved in emissions reduction

A new atomic-scale pointer reveals the subtler molecular interactions at play during catalysis.

Compass-inspired 'pointers' absorbed into porous catalysts can pinpoint the atoms in a surrounding material with the weakest force fields. The pointer was designed by Fei Wei's team at Tsinghua's Department of Chemical Engineering, and their findings were published in *Nature* in April, 2021[1].

The faint forces being measured, which are known as van der Waals interactions, could play a role in the efficiency of catalysts used to help reduce harmful emissions released by industry using fossil fuels. "Explaining the van der Waal interaction mechanisms could help us design better catalysts and improve the conversion rate and selectivity of reactions," says Wei.

His team used an aromatic hydrocarbon, *para*-xylene, as a molecular pointer.

The *para*-xylene molecule contains two opposite methyl groups that make a long axis across the channel," explains Wei. These will 'point' to the atoms around it with the lowest energy.

In the study, the *para*-xylene molecules were absorbed in to the straight channels that make up some of the porosity of an aluminosilicate mineral. The mineral, a zeolite catalyst known as ZSM-5, is widely used in processes for the petrochemical industry as well as automotive and industrial emissions reduction. "MFI-type zeolites, such as ZSM-5, have straight channels that can only accommodate a single *para*-xylene molecule at a time," says Wei. Previous studies had shown that the long molecular axes of the pointer would end up almost parallel to the straight channel, unless there were other host-guest interactions at play.

In a follow up study in 2022[2], Fei Wei's team used a benzene molecule (yellow and lilac) as a probe to better understand the structural flexibility of zeolite catalyst ZSM-5's pores (the blue and purple represent ZSM-5's crystal structure, with the black circles representing the pores).

In the zeolite channel, the pointer will orient towards the nearby atoms guided by van der Waals interactions with the lowest energy, in this case the atoms of silicon and oxygen make up the walls of the zeolite channel. The pointer also adjusted to changes of the van der Waal interactions that corresponded to changes in channel geometry.

Fei Wei (pictured) has been studying the potential of molecules, para-xylene and benzene, for use as pointers to surrounding atoms with low van der Waals forces. On screen benzene molecules (the white dots on the screen) are confined within the porous channel of the industrially useful zeolite catalyst, ZSM-5 (purple and blue on screen). They line up with the lowest energy atoms.

Enabled by new technologies

When the team measured the orientation of the *para*-xylene pointers, they used advanced microscopy imaging technology. Wei stresses that advances to integrated differential phase contrast scanning transmission electron microscopy (iDPC-STEM) is what has made the recent finding possible.

While high-energy electron beams used in transmission electron microscopy are an effective way to characterize atomic-scale structures, "it's difficult to study host-guest interactions at atomic scales for porous materials, which are extremely sensitive to electron beams and often overshadow host materials", explains Wei. iDPC-STEM enabled good contrast between light and heavy elements at extremely low electron beam doses, he says.

Pointer possibilities

Ultimately, imaging the orientations of *para*-xylene pointers will provide information on both the spatial distribution and real-time changes of van der Waals potential fields in porous material channels, says Wei.

Recently, using *in situ* electron microscopy, the team also imaged the subcell topological flexibility of the pores in ZSM-5 zeolites[2], using the industrial chemical benzene as the probe molecule. "Zeolites are catalysts widely used in industry," explains Wei. "Benzene, and its derivatives are intermediates in many catalytic reactions, so the van der Waals interactions between the two are closely related to catalytic mechanisms."

This method could, for example, help researchers better understand reactions, such as the transformation of methanol into formaldehyde and formic acid, which are widely used in many building materials. Wei adds that the hydrocarbons used in many industrial-important processes, including methanol conversion, consist a lot of benzene ring structures, which are able to be imaged in the same way.

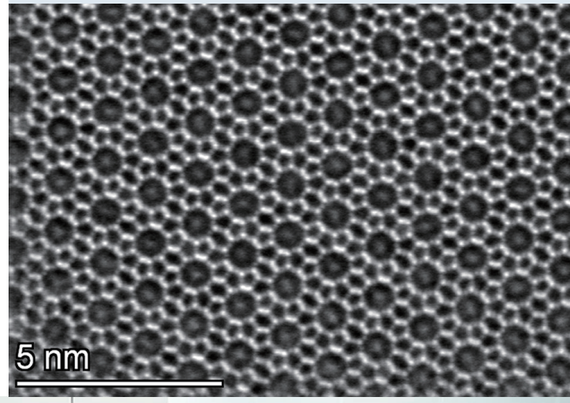
Other organic molecules, such as homologues of aromatics, can also be confined and imaged in this or other size-matching porous frameworks. "Thus, this work may provide a general method to investigate host-guest interactions in a series of organic/inorganic systems," says Wei. "This is also an intuitive way to interpret van der Waals interactions from images, which allows us to understand van der Waals interactions from another angle."

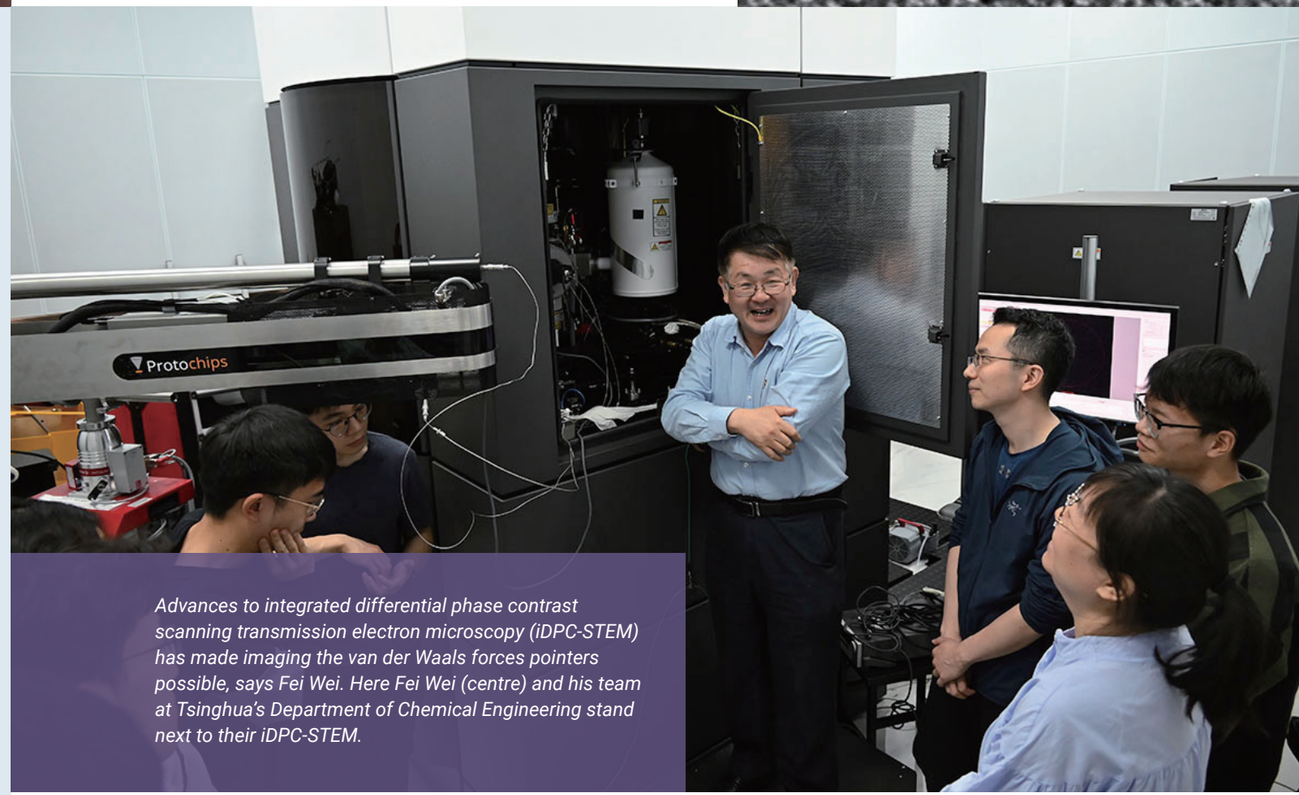
References

[1] Shen, B., Chen, X., Wang, H., Xiong, H., Bosch, E. G. T. *et al*. A single-molecule van der Waals compass. *Nature* **592**, 541–544 (2021) https://doi.org/10.1038/s41586-021-03429-y

[2] Xiong H., Chen, X., Wei, F., Wang, H., Qian, W. *et al*. *In situ* imaging of the sorption-induced sub-cell topologic flexibility of a rigid zeolite framework. *Science* **376 (6592)**, 491–496 (2022) https://doi.org/10.1126/science.abn7667

An image of the crystal structure of a zeolite catalyst known as ZSM-5. The aromatic hydrocarbon, para-xylene, can be seen inside the decagon shape of the ZSM-5 channels/pores[1].





Advances to integrated differential phase contrast scanning transmission electron microscopy (iDPC-STEM) has made imaging the van der Waals forces pointers possible, says Fei Wei. Here Fei Wei (centre) and his team at Tsinghua's Department of Chemical Engineering stand next to their iDPC-STEM.

Up to 70% of Aedes mosquites were found to prefer to feed on mice infected with dengue and Zika viruses.

Dengue and Zika viruses make their victims smell appealing to mosquitoes

These viruses alter a host's skin microbiota to produce a mosquito-attracting molecule. A vitamin A supplement can reverse the effect.

As the virus behind the COVID-19 pandemic has proven, pathogens are adept at doing what they can to replicate and spread. Scientists have now discovered a new ruse employed by the viruses responsible for dengue fever and Zika fever – when they infect people, they make them smell more appetizing to hungry mosquitoes, which makes infected individuals more likely to be targeted.

Mosquitoes are attracted to the change in smell, says Gong Cheng, a microbiologist at Tsinghua University in China, and co-author of a new paper published in the journal *Cell*[1].

The good news, however, is that the effect can be negated with a dose of a Vitamin A derivative.

Researchers have known for decades that people who are ill can give off body odours that differ from those of healthy individuals, because certain types of pathogens, such as malaria, change a host's microbiota, prompting bacteria on the skin to release unique molecules. But whether Zika and dengue —mosquito-borne diseases that infect up to 400 million people annually — had similar odour-altering capabilities to the malaria pathogen has remained a mystery until now.

To investigate, Cheng and his colleagues at several Chinese labs placed Zika-infected and healthy mice into separate enclosures. When they piped air from each into a cage filled with mosquitoes, they found that 65–70% preferred to feed on the Zika-infected animals. Similar results were found with dengue-infected mice.

Smells like oranges?

A chemical analysis of the air revealed that a molecule called acetophenone, which has an odour redolent of oranges, was behind the newly appealing scent. Flavivirus-infected mice were found to produce approximately 10 times more acetophenone than healthy mice.

This happens in humans too, the researchers discovered. When dengue patients had their armpits swabbed, and the collected odours were dabbed on the backs of volunteers' hands, the latter were more likely to attract mosquitoes than healthy participants who had not been wiped.

"Dengue patients release higher levels of acetophenone," says Cheng. "Acetophenone acts as the potent odorant for mosquito attractiveness."

The volatile molecule has many applications — as a fragrance in soaps and perfumes, a flavoring agent in foods and a solvent for plastics and resins. It is also found in some cheeses and bananas. Acetophenone is normally produced in small quantities by bacteria that reside on human and mouse skin. Antimicrobial peptides called resistin-like molecule-α (RELMα) usually keep their numbers in check. "However, Zika and dengue viruses largely suppress the expression of RELMα, favouring the proliferation of acetophenone-producing bacteria over others in the host skin," says Cheng. This, in turn, alters the victim's smell.

Feeding the sick mice with isotretinoin — a vitamin A derivative widely used to treat acne and other skin conditions — restored the antimicrobial peptide to near-normal levels and lowered the amount of acetophenone the animals exuded, making them less attractive to mosquitoes.

The findings suggest "a novel avenue" to combat dengue and Zika outbreaks, says Cheng. But using vitamin A supplements as a treatment still has to be tested in humans — something he and his colleagues plan to dolater this year in Malysia, where dengue has been endemic for more than four decades.

Reference

[1] Zhang, H., Zhu, Y., Liu, Z., Peng, Y., Peng, W *et al*. A volatile from the skin microbiota of flavivirus-infected hosts promotes mosquito attractiveness *Cell* **185**, 2510–2522 doi: 10.1016/j.cell.2022.05.016.

Gong Cheng (far right) is working on testing new ways counteract a mosquito-attracting skin smell on those infected with dengue and Zika.

Self-taught AI detects disorders from head scans

This intuitive AI can sort through scans to diagnose stroke, brain haemorrhage, brain tumors and skull fractures.

A Tsinghua team has developed a self-taught deep learning system that can detect four different conditions – stroke, brain haemorrhage, brain tumors and skull fractures. Their artificial intelligence (AI) performed at 96% accuracy, the same rate as radiologists[1].

Qionghai Dai, a professor at Tsinghua's Department of Automation, explained that the AI learned to read head scans without a great deal of guidance from radiologists.

Growing demand

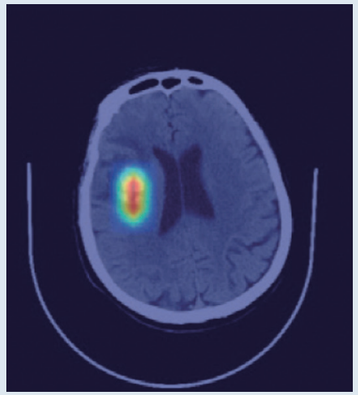
Stroke, brain haemorrhage, brain tumors and skull fractures alter the structure of the head and brain, increasing the risk of permanent brain damage or death, explains Dai. Since it was developed in the 1970s, computed tomography (CT) scanning has used X-rays to produce multiple cross-sectional images of the brain to assess these types of abnormalities. Hundreds of millions of CT scans are performed every year, putting increasing pressure on doctors and radiologists. "Analysing all these images is challenging and labour-intensive," says Dai, "and many sites lack experienced radiologists to do this extra work."

Artificial intelligence researchers have been testing whether machines could be taught to detect disorders related to the head. Supervised learning demands vast amounts of annotated training data, in which specialists have already labelled the affected areas, says Dai. "This can be very expensive, so most studies can only build small datasets. This results in AIs that can only diagnose one or two specific diseases, and only perform well within the walls of one medical centre," he says.

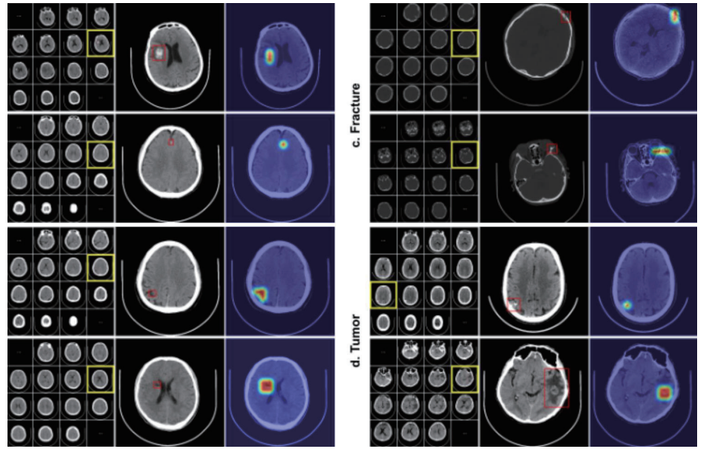
In recent years, a few studies have achieved the gold standard of above 95% diagnostic accuracy, but only for specific disorders, such as brain haemorrhages, he adds. These AIs were trained on between 1,000 and 4,000 CT scans that had all been heavily annotated by radiologists.

However, it is possible to build considerably larger training datasets without any expert guidance by using weak annotation, whereby messy or imprecise information, such as written descriptions, are used to generate labels, says Dai.

It was using this technique that he and his team developed their annotation-free deep learning system.



Tsinghua's Institute for Brain and Cognitive Sciences has helped create an AI that uses less man power to learn to detect a number of conditions linked to the head using computed tomography images. These conditions include stroke, brain haemorrhage (pictured), brain tumors and skull fractures.



Hungry AIs

But this type of deep learning is extremely data-hungry, using multiple layers of computations that allow the model to learn by itself. To develop their system, the researchers collected more than 100,000 CT scans, along with their relevant diagnostic reports.

The scans, which sometimes revealed multiple disorders, included roughly 20,000 haemorrhages, 25,000 strokes, 19,000 fractures, 3,000 tumours, and 45,000 normal cases.

The team used automatic keyword matching on the reports to generate labels for the scans, which they fed into their deep learning algorithm, RoLo (Robust Learning and Localized Lesion). This is called 'weakly supervised' machine learning, as it draws on disorganised and imprecise information to create training data. "Weak annotation can lead to wrong labels in training data and working at the scan-level labels means it does not show the specific location of relevant head lesions," says Dai. "But it is much easier to create a large-scale training set this way, so we can shift the cost from expert labelling to novel AI algorithm design," he says. Bigger data sets and better algorithms will help reduce the influence of errors, he adds.

To check whether their AI worked in a range of settings, Dai's team tested it on about 3,000 CT scans taken from one hospital in China; 1,500 from several different hospitals; 1,500 from different scanning set-ups; and 500 from a dataset from India. They found their AI could correctly diagnose and distinguish between the four head disorders equally well across the different datasets. It averaged more than 96% accuracy, matching the performance of four radiologists who assessed the scans by eye.

Having tested RoLo extensively in the lab, Dai and his team are keen to iron out the logistics and legalities of bringing their new AI into hospitals. "We want to make an affordable and accurate AI system that can be used routinely in clinics and hospitals around the world to help research and diagnose head disorders," says Dai. "Now we know that we can build an AI for diagnosing four different disorders, we are keen to develop new AI theories, design state-of-the-art AI algorithms, and build a practical AI system that can detect even more conditions."

Reference

[1] Guo, Y., He, Y., Lyu, J., Zhou, Z., Yang, D. *et al*. Deep learning with weak annotation from diagnosis reports for detection of multiple head disorders: a prospective, multicentre study *Lancet Digital Health 2022* **4(8)**, E584-E593 (2022) doi: 10.1016/S2589-7500(22)00090-5

Brain patches linked to nuanced voice interpretation

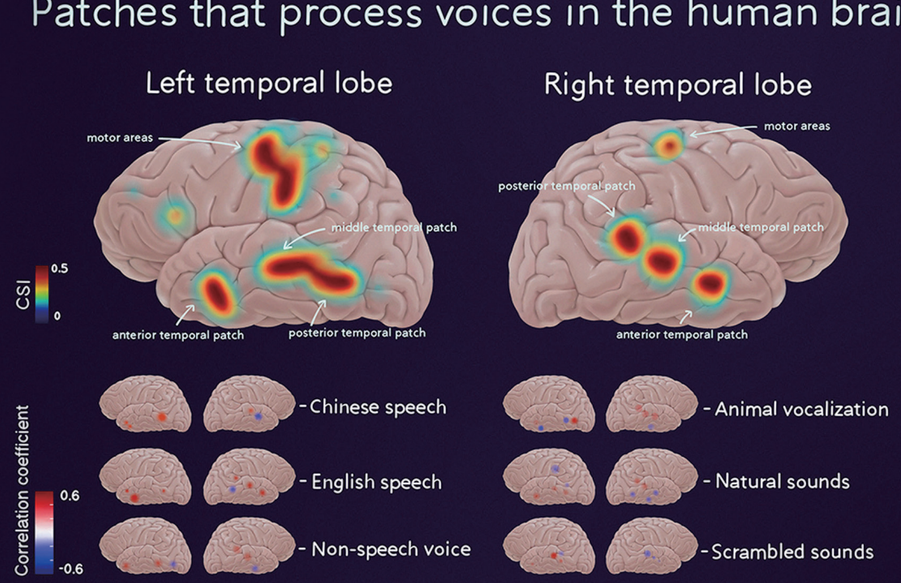
Six newly identified sites in the temporal lobes may be key to how the brain extracts rich information from the human voice.

People have a remarkable ability to perceive different information from voice alone, such as a speaker's identity, meaning, and emotional state, says Xiaoqin Wang, a professor of biomedical engineering at Tsinghua University and the head of Tsinghua Laboratory of Brain and Intelligence. "When we pick up the phone, we often know who's calling after hearing only a few words."

However, the question of how our brains extract and process such information is one that has eluded neuroscientists for years. Finding the answer, Wang says, could help us better understand why some people aren't good at interpreting social cues.

In a paper published last December in the *Proceedings of the National Academy of Sciences*, Wang and his collaborators describe how they found specialized regions within the brain that are responsible for processing the voices we hear.

The regions — which they call 'voice patches' — are located in the superior temporal gyrus (STG) of the temporal lobe, the part of the brain that sits just above ear level and is associated with sensory processing. There are three patches in a row in each hemisphere.



The brains of five people showed the same patterns of increased electrical activity in response to human voices measured by a catergory selectivity index (CSI). Motor areas were shown to co-activate.

Linked voice specialists

"The significance of the voice patches is that they form a network of connected brain regions that are specialized in processing human voices," explains Wang. This interconnectivity remains whether a person is actively paying attention to a sound or not.

His team observed this by studying five people with epilepsy who had electrodes placed on the surface of their brains prior to surgery designed to identify the source of their seizures. The researchers measured the electrical activity of the patients' brains as they listened to six different types of sounds — half involved voices in native Chinese and English, while the other half were non-voice sounds such as animal vocalizations and noises from nature.

When listening to the former category, the patients' brain activity was significantly higher, implying that the patches are more selective for voice over non-voice sounds, says Wang. "Voices are a special class of sounds… different from environmental ones, instrumental music ones, or sounds made by animals."

To arrive at this finding, his team also took a markedly different approach to testing. Traditionally, researchers use functional magnetic resonance imaging (fMRI) or other types of scanners to see which part of the brain is being used as a patient carries out various tasks. But these techniques only measure neural activity indirectly and "have limited capacity to reveal the brain's response to the dynamic properties of human voices in real time," says Wang.

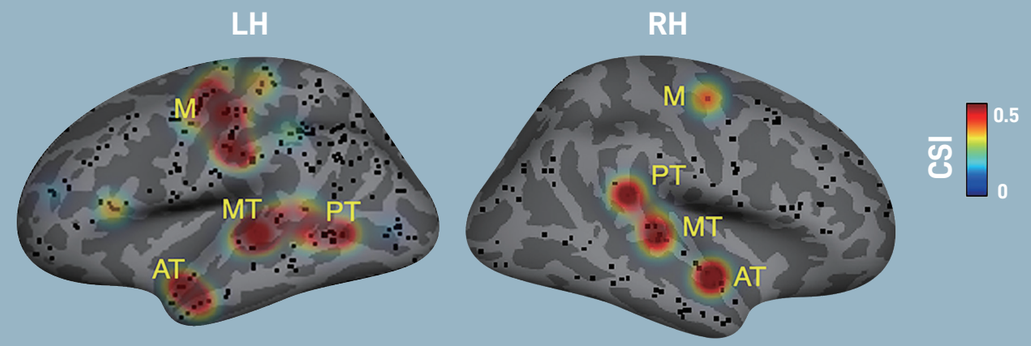
Instead, his team used electrocorticography, a type of electrophysiological monitoring that uses electrodes placed directly on the exposed surface of the brain to record electrical activity directly from the cerebral cortex.

The group will next study how the brain extracts and processes emotional information that voices can carry. It's fascinating work, says Wang, because new knowledge can have tremendous implications for understanding how we speak, how we hear, and how we interact with others across a lifetime.

Reference

[1] Zhang, Y. *et al*. Hierarchical cortical networks of "voice patches" for processing voices in human brain. *PNAS* **118 (52)**, e2113887118 (2021) doi: 10.1073/pnas.2113887118

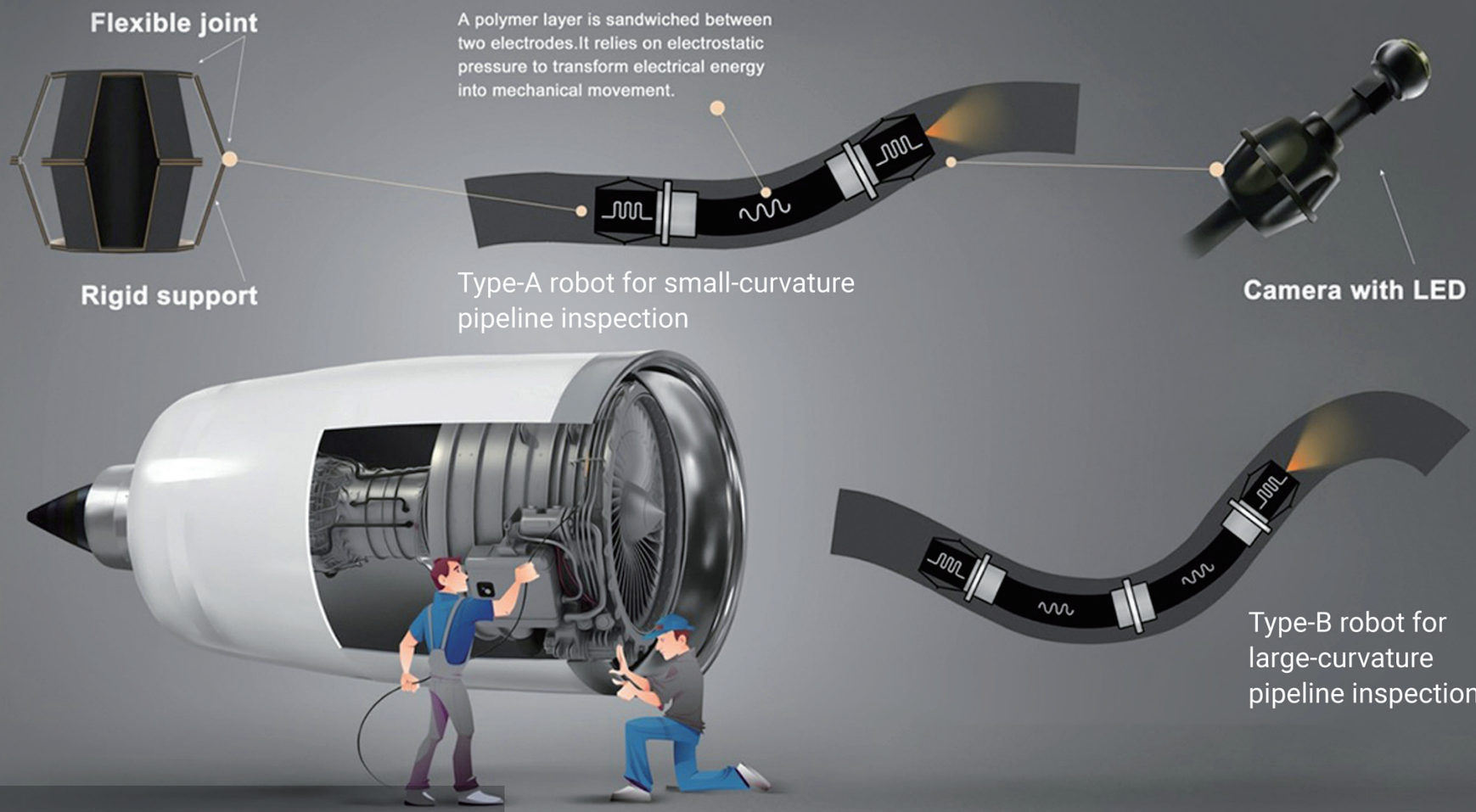
Three areas on the left temporal lobe and three areas on the right temporal lobe were shown to be preferentially activated by voices over non-voice sounds. The three areas have been dubbed the posterior temporal patch (PT), middle temporal patch (MT) and anterior temporal patch (AT). Motor areas (M) were also shown to co-activate.



RESEARCH FEATURE

Soft robots take on hard work

A robotics expert is helping her inventions navigate through difficult, tight spaces using unique soft materials that contract and expand on demand.



Huichan Zhao and her collaborators are creating soft robots that use similar movement techniques to earthworms for potential use in inspecting small pipelines, such as those found in aircraft engines.

In the last few years, oil and gas companies have begun to rely on robots to travel miles of undulating pipelines checking for weaknesses, cracks, and blockages.

But it's been much harder to make mechanical robots small enough to squeeze through the centimetre-wide tubes commonly found in everything from aircraft engines to oil refinery machinery.

Huichan Zhao, a mechanical engineer at Tsinghua University in China, thinks soft robots, without wheels or other chunky components that can't fit through a gap or squeeze around a tight corner, could be the solution.

Soft robots often attempt to copy the motion of nature's soft structures, such as elephant trunks and the tentacles of an octopus, explains Zhao. Soft structures can often move in more complex ways than conventional robots with joints, she says.

Earlier this year, Zhao and her collaborators published the details of a soft robot designed to mimic the movement of earthworms, which could be used to perhaps inspect the narrow pipes found in machinery such as aircraft engines. One day, she hopes her earthworm-inspired robot could replace the fibre-optic cables typically used to inspect these pipes today.

"Using fibre optics to see inside pipes requires a skilled engineer to manually control the process," she explains. "Using a robot that navigates the pipe itself saves time and effort."

Worming through

An earthworm travels forward using a physical process called peristalsis, which relies on the rhythmic contraction and relaxation of muscles in a series of connected segments. Ring-like muscles around the worm's diameter can change its body thickness to either swell and grip the inside of a tunnel or shrink to pass through. Longitudinal muscles along the length of the creature's body push the worm forwards or backwards.

So, if an earthworm fixes its rear ring muscles against a tunnel's insides and then stretches its longitudinal muscles to push forwards, followed by fixing its front ring muscles and then contracting its longitudinal muscles again, its body nudges forward.

Most importantly for soft robot design, because an earthworm moves purely through muscle expansion and contraction, it doesn't need any complicated moving parts and mechanisms. This makes it relatively easy for scientists to copy.

To mimic this movement pattern, Zhao focused developing smart materials called dielectric elastomer actuators that can squeeze and relax in response to an electric supply being turned on and off.

These smart materials sandwich a polymer layer between two electrodes and rely on electrostatic pressure to transform electrical energy into mechanical movement.

Using dielectric elastomer actuators that work in different directions when stimulated by electricity to mimic the earthworm muscles, Zhao could build a robot that uses the same strategy as an earthworm to move through a narrow pipe: anchoring one end against by expanding to brace against the pipeline walls, and then extending along it.

By attaching a small camera to the front of the robot, users can check the insides of the pipe as the robot nudged along.

Published in the journal *Science Robotics*[1], the soft robot is a demonstration of how the concept could work, but many details must be ironed out before it could be used in practice.

For instance, because the electricity is supplied to the robot through trailing wires, this increases drag and might prevent the robot from making headway through some pipelines. A better design would rely on portable high-powered batteries, says Zhao.

"As far as I know, there are no such robots in use. Many challenges need to be overcome, such as how to effectly connect an energy supply, and improve controllability and reduce cost," she says. "I think, it still needs five to ten years of fundamental research."

Rapid rise for robotics researcher

Zhao is still in her 30s, having graduated with a double degree in mechanical engineering and economics from Tsinghua in 2012. She then carried out postgraduate studies and training in the United States, including time working on using integrated sensors to improve robot touch sense at Cornell University in the United States, and later at the Microbiotics Laboratory at Harvard University, also in the US. When she returned to Tsinghua in 2018, she was one of the youngest faculty members at the time.

Her research with robots is not confined to pipelines. With collaborators, she has previously developed a tiny flapping robot and eventually got it to fly. And in early 2020, she and other team members developed an early throat swab sampling robots in response to the outbreak of the COVID-19 pandemic. The swabbing robot looks more like a conventional robot: a seven-jointed robotic arm and a small robotic hand that can grab cotton swab. It was designed to relieve the burden on human samplers, reducing the risks of infection and contamination via the sampling process, explains Zhao.

This soft robot that uses the same movements as an earthworm to move through a narrow pipe – anchoring by expanding its front or back sections to brace against the tunnel or pipe walls, and then extending its middle sections to move forward.

Healthcare should be a useful arena for soft robots, she adds. "They could be used as surgical robots," she notes. "I think they could become quite desirable, as they would do less harm to tissues than hard instruments."

So, while robots that look like humans often receive the most of the attention, it could be the small soft robots inching around our pipelines or in the body that really have an impact on day to day life.

Huichan Zhao (right) tests one of her robotic creations

Reference

[1] Tang, C., Du, B., Jiang, S., Shao, Q., Dong, X., *et al*. A pipeline inspection robot for navigating tubular environments in the sub-centimeter scale *Science Robotics* **7(66)** (2022) doi: 10.1126/scirobotics.abm8597

Does social stress make us more forgetful?

Recent findings show that negative or positive social environments stimulate a protein that temporarily makes some memories harder or easier to access.

"It is curious how sometimes the memory of death lives on for so much longer than the memory of the life that it purloined," wrote Arundhati Roy in her Booker Prize winning novel, *The God of Small Things*. Why some of our recollections remain close to the surface, while others are buried deeper, also intrigues researcher, Yi Zhong.

"The ability to flexibly remember and forget are both important for our mental health," Zhong points out. Post-traumatic stress disorder (PTSD), for example, is linked to an inability to silence traumatic memories. Understanding on a molecular level how the brain activates memories might bring new treatment options into play, Zhong notes. A recent mouse study by his group has even suggested that brain-administered drugs or proteins might be able to help tweak this process.

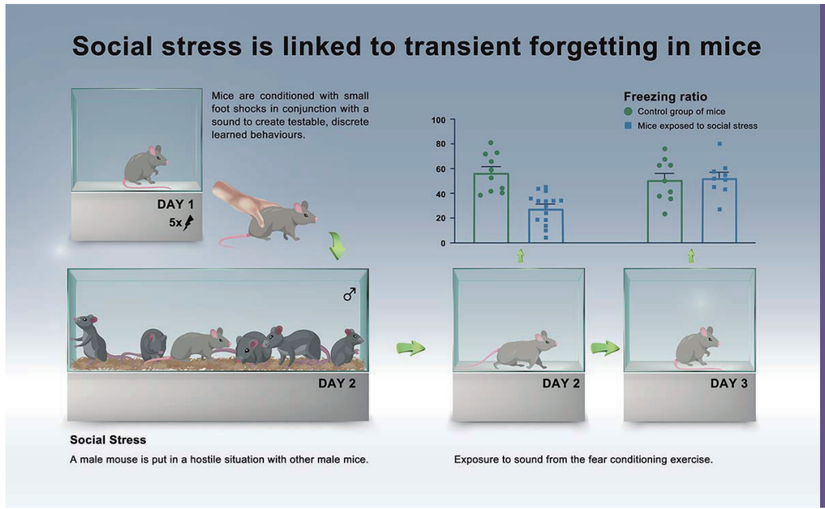
This latest work, done at Tsinghua's School of Life Sciences, focussed on how social stress or reward might affect the brain's internal filing system. Specifically, Zhong looked at what neuroscientists call memory states.

The most easily recalled memories are those in a *latent state*: for example, the names of the vegetables you need to buy for dinner tonight. More deeply buried are *silent state* memories – the recollection of a particular meal as a child, perhaps – which the brain usually only converts to more accessible latent state memories after an external cue, such as a smell.

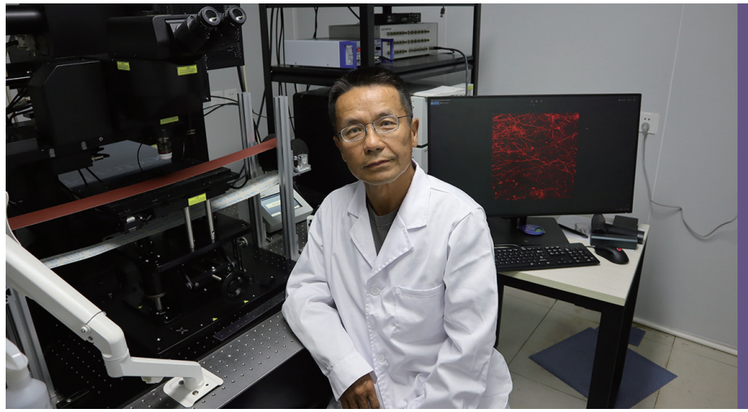
Humans and other animals evolved this storage system to cope with the world's complexity, says Zhong. "Remembering everything is not a good strategy for an animal living in an ever-changing environment," he points out. It would be overwhelming to process lots of memories all the time, he explains, and, not all experiences from the past are useful lessons for the present moment. "The ability to switch the states of memory is how animals achieve flexible and dynamic behaviours," he explains.

Stress-head

Researchers think different memory states are the result of the number and strength of the connections between the synapses of adjoining bundles of



A difference in the freeze responses between mice exposed to social stress and control mice suggest that social stress causes a disruption in recent memories.



Yi Zhong is a professor at the School of Life Sciences at Tsinghua University.

brain cells – called engrams. Stronger connections tend to mean the memory is more easily accessed – a latent state – while damaging the connections might switch a memory to a silent state. Thus, many memory studies look at how the brain makes and breaks these synaptic connections.

In Zhong's recent mouse study, published in *PNAS* in April 2022[1], the effect of social stress and reward in reinforcing or silencing older memories was explored.

Initially the group used fear conditioning – small foot shocks in conjunction with a context, such as distinct smell, sound, and floor texture to create testable, discrete learned behaviours in the mice. After this, social reward was invoked in some of the mice by allowing a male mouse to mix with females, and stress, by temporarily putting an animal in a hostile situation with other males.

After the mice were exposed to social stress or reward, Zhong's team were able to identify significantly different recall levels of fear conditioned memory between the mouse groups by observing freeze responses linked to the context from the conditioning exercise. They also used virus-delivered, fluorescent protein to identify and track indications of changes in the silent and latent states of the engrams linked to the fear memories.

The results suggest that the sensation of reward felt by the male mice mixing with the females helped the males convert memories from a silent to a latent state. And, *vice versa*, social stress encouraged latent state memories to switch to the silent state, which the researchers described as "transient forgetting" as it didn't show up 48-hours after the exposure to stress.

To investigate the underlying mechanism, Zhong and his colleagues looked at activity in the mouse hippocampus, a part of the brain strongly associated with memory. Specifically, they looked at the activity levels of a protein called Rac1, which is believed to play a role in helping to organise connections between brain cell synapses. "Rac1 is known to be involved in the forgetting of memories through regulating synaptic structures," explains Zhong.

Their experiments showed that social reward suppressed the protein, while social stress increased its activity. "Hippocampal Rac1 activity is definitely sensitive to emotional stimuli," says Zhong.

Given their earlier observations the scientists concluded that lower levels of protein activity might be involved in helping the animals retrieve memories, switching silent state memories to the latent state. And the reverse might be true.

The group then bolstered their hypothesis via a number of routes, explains Zhong. They showed that low Rac1 activity levels do rescue memories. The group tested this by artificially silencing engrams and observing, after the injection of Rac1 inhibitors, silenced engram memory recall in memory tests. Another showed a Rac1 inhibitor prevented the social stress-induced memory disruption observed in a non-Rac1 inhibited group of mice.

"We believe Rac1 in the hippocampus is a connector between the emotion system and memory system, linking the emotional state and memory state," Zhong concludes.

Antibiotic boost

The discovery of this possible connection offers an opportunity, says Zhong. Researchers could manipulate activity levels of Rac1 as an indirect way to trigger deliberate switches in memory state.

In mice, Zhong's group looked at how raising hippocampal *RAC1* activity via injections of an antibiotic called anisomycin, which inhibits protein synthesis, converts latent memories to the silent state. In doing so it recreated the effects of social stress.

Injection of the *RAC1* inhibitor 'Ehop016', had the opposite effect and encouraged state switching from silent to latent memories. This recreated the effects of social reward.

In theory, such interventions to stimulate memory state switching, in either direction, could help address some of the difficulties seen in people with PTSD. But they could also address the memory difficulties experienced by those with autism spectrum disorders and Alzheimer's disease too, says Zhong.

"The abnormal switching of memory states may contribute to many neural disorders," he says.

Episodic memory, the memory of everyday events able to be explicitly recalled, seems to be unduly silenced in Alzheimer's disease patients, he points out. And in 2016, the team showed that flies with five autism susceptibility gene mutations were unable to forget previously formed memories via the activation of the *RAC1* gene. This suggests, says Zhong, that people with autism could be showing lower memory flexibility because they find it harder than other people to silence an original memory.

Work in people is more challenging because some of the techniques used to manipulate Rac1 and monitor the effects in mice at a molecular level are not suitable for human studies. Injecting and expressing fluorescent proteins requires access to the brain through the skull. As a result, most memory research in people is much less detailed. Researchers have found psychological stress can decline the accessibility of episodic memory, but have been limited in their ability to observe the molecular processes.

Still, Zhong says there is some encouraging evidence that many of the findings on memory state switching in animals can be applied to people. "Our recent work revealed that the hippocampal Rac1 activity in Alzheimer's disease patients is significantly elevated, which is consistent with our finding of the relationship between memory states and Rac1 activity," he says.

"This work indicates that our findings in the animal studies are also relevant for humans. But direct evidence is still required from further investigations."

References

[1] Lei, B., Lv, L., Hu, S., Tang, Y. & Zhong, Y. Social experiences switch states of memory engrams through regulating hippocampal Rac1 activity *PNAS* **119 (15)**, e2116844119 (2022) Doi: 10.1073/pnas.2116844119

[2] Dong, T., He, J., Wang, S., Wang, L., Cheng, Y. *et al*. Inability to activate Rac1-dependent forgetting contributes to behavioral inflexibility in mutants of multiple autism-risk genes *PNAS* **113 (27)**, 7644-7649 (2016)

Yi Zhong's team at Tsinghua's School of Life Sciences study the neural mechanisms of learning and memory using genetics, electrophysiology, behavior and imaging.

Gene find bolsters claim that reproductive fitness in youth leads to faster aging later in life

The discovery of a key DNA sequence adds weight to a theory on the costs of reproduction.

A theory that some genes provide benefits in early life — allowing organisms to have more offspring — but detrimental effects in later life, leading to aging, has been given a boost by Tsinghua University researchers who have found one such a gene.

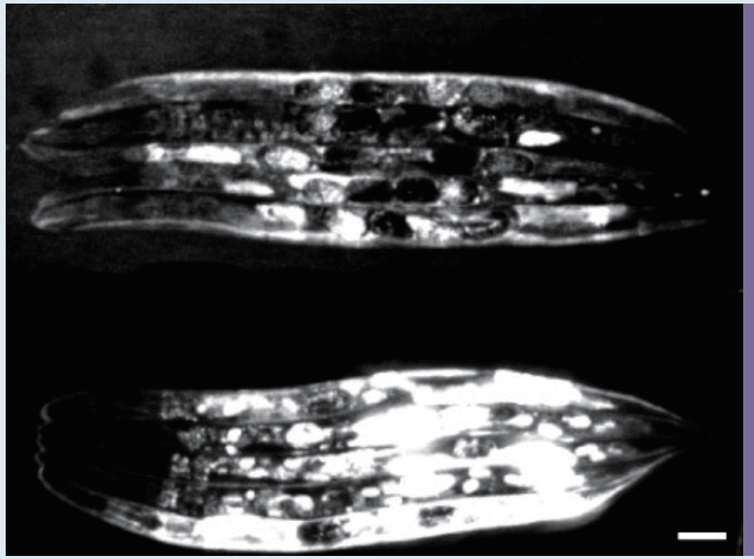
This finding in a tiny nematode worm lends weight to the so-called 'antagonistic pleiotropy' theory of aging, which was proposed in 1957 and posits that there is a trade-off between early reproductive fitness and lifespan[1]. The results have been published in the journal *PNAS*[2].

Under this theory, aging is driven by pleiotropic genes — these influence two or more seemingly unrelated physical traits which offer a reproductively useful advantage early in life, but later become detrimental. But until now the theory has lacked direct genetic evidence.

"We think antagonistic pleiotropy is either very common or ubiquitous throughout the animal world," says lead researcher behind the study, Professor Guangshuo Ou. Quantitative genetic studies and studies of naturally segregating polymorphisms, have hinted at the trade-off between traits, but other explanations couldn't be ruled, he explains. "Compelling evidence of antagonistic pleiotropy at an individual gene resolution remains scarce."

The researchers made their breakthrough by studying a nematode worm called *Caenorhabditis elegans*, which is commonly used as a model organism.

C. elegans adapts rapidly when under environmental stress to enhance its chance of survival and ensure growth and reproduction. For instance, in response to an absence of food during development, worms turns into a potentially long-lived 'dauer larvae' incapable of reproduction. But on refeeding, they revert to their former state.



Two Caenorhabditis elegans nematode worms 60 mins after they have been fed after being starved. The top worm is a wild type and shows less translation of proteins associated with egg yolks than the bottom, in which the trl-1 gene is deleted.

By studying the biochemistry of worms recovering from starvation, Ou's team have identified a likely antagonistic pleiotropic gene that directs nutrients to egg development within well-fed worms.

Feeding offspring ages parents

By performing genetic analyses of *C. elegans* following six days of starvation, they found that a gene dubbed *trl-1* was producing more proteins after refeeding. To test if *trl-1* was linked to reproduction and lifespan, they created a strain of *C. elegans* devoid of the gene, and found that they "had increased brood sizes and shortened lifespans," Ou says.

Furthermore, his team also showed that genes which help produce a yolk protein, called vitellogenin, were upregulated in the modified worms.

"The loss of *trl-1* upregulated the translation of vitellogenin, which produces copious yolk to provision eggs," Ou explains. But the overexpression of vitellogenin also "is also known to reduce the lifespan in *C. elegans*[3]," he adds.

The researchers then went on to show that the protein produced by *trl-1* works to inhibit the translation of vitellogenin messenger RNA to halt the production of the egg yolk protein.

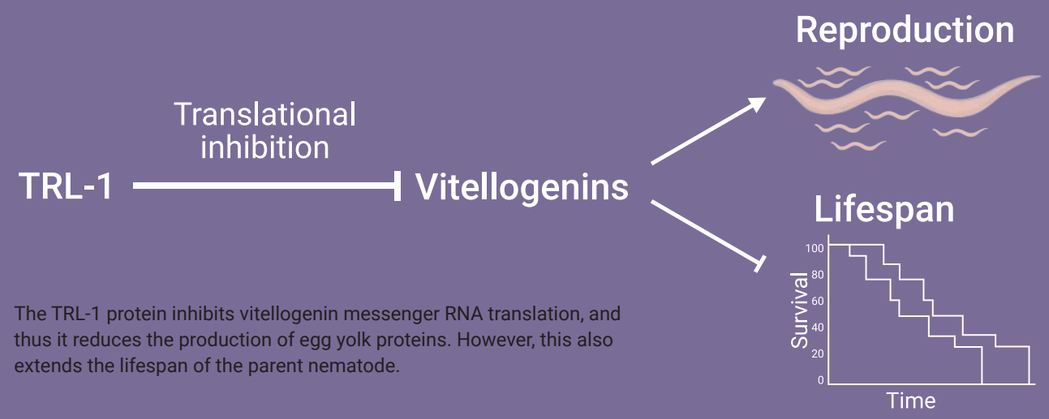
The end result is that nutrients provided to developing eggs are limited, but the lifespan of the parent nematode is extended because it is putting fewer resources into egg development.

"These results indicate that *trl-1* functions as an antagonistic pleiotropic gene that regulates the reproduction-longevity trade-off by optimizing nutrient production for eggs," says Ou.

He adds that while analyses had not previously identified similar gene sequences in mammals, "functional gene sequences, rather than protein sequences, are more likely to be preserved".

The team is now searching for other genes involved in recovery from starvation, which might also be linked to a trade-off in reproductive fitness and lifespan.

"Understanding *trl-1* has already helped to clarify one aspect of how the genome shapes the aging process, and this will help us study of the genetic factors that influence longevity and age-associated diseases," he says.



The TRL-1 protein inhibits vitellogenin messenger RNA translation, and thus it reduces the production of egg yolk proteins. However, this also extends the lifespan of the parent nematode.

References

[1] Williams, G. C. Pleiotropy, Natural Selection, and the Evolution of Senescence. *Evolution*, **11**, 398-411 (1957).

[2] Wu, D., Wang, Z., Huang, J., Huang, L., Zhang ,S. *et al*. An antagonistic pleiotropic gene regulates the reproduction and longevity tradeoff. *Proceedings of the Notational Academy of Science U S A*. **119(18)**, e2120311119 (2022). doi: 10.1073/pnas.2120311119

[3] Seah, N., E., de Magalhaes Filho, C., D., Petrashen, A., P., Henderson, H., R., Laguer, J., *et al*. Autophagy-mediated longevity is modulated by lipoprotein biogenesis *Autophagy* **12(2)**, 261–272 (2016) doi: 10.1080/15548627.2015.1127464

Antibodies show potential to boost fertility for women with ovarian failure

Mouse models show that an antibody therapy could normalise reproductive performance.

A Tsinghua University team led by Professor Bai Lu has recently shown that administering an antibody called Ab4B19 promotes the development of ovaries and enhances fertility in mouse models with a condition called premature ovarian failure.

Premature ovarian failure is a leading cause of infertility, affecting 1–5% of women aged under the age of 40, explains Lu. The disease occurs when the ovaries aren't producing typical amounts of the hormone estrogen, or releasing eggs regularly. However, the mechanisms underlying the condition remain poorly understood, and there is no effective treatment.

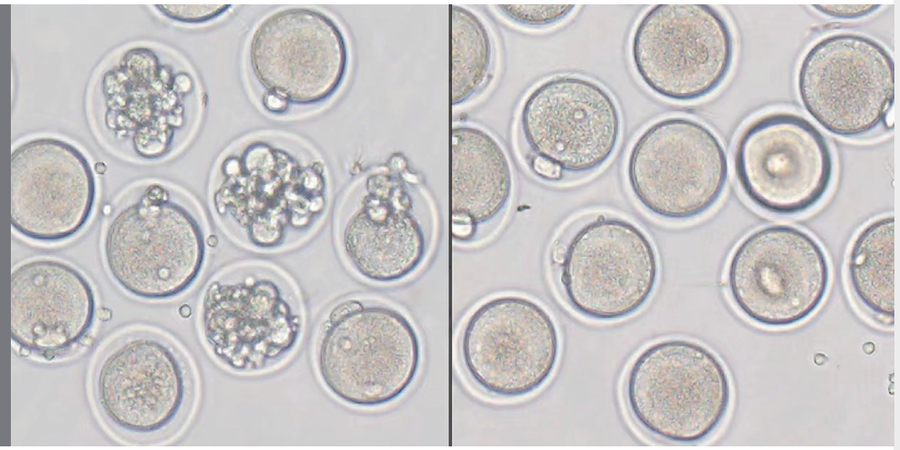
Remarkably, treatment with the Ab4B19 antibody, which is also known to stimulate neuronal growth, completely reversed deficits in ovarian follicles, which are small sacs in the ovaries that release eggs and hormones. The treatment also normalized ovarian hormones and restored the number and quality of immature eggs in the mouse models[1].

In the study, Ab4B19 was shown to penetrate ovarian follicles via the bloodstream and activate a key receptor on brain-derived neurotrophic factor (BDNF) proteins, says Lu. The receptor, tropomyosin receptor kinase B (TrkB), regulates hormones during follicular development, among other things.

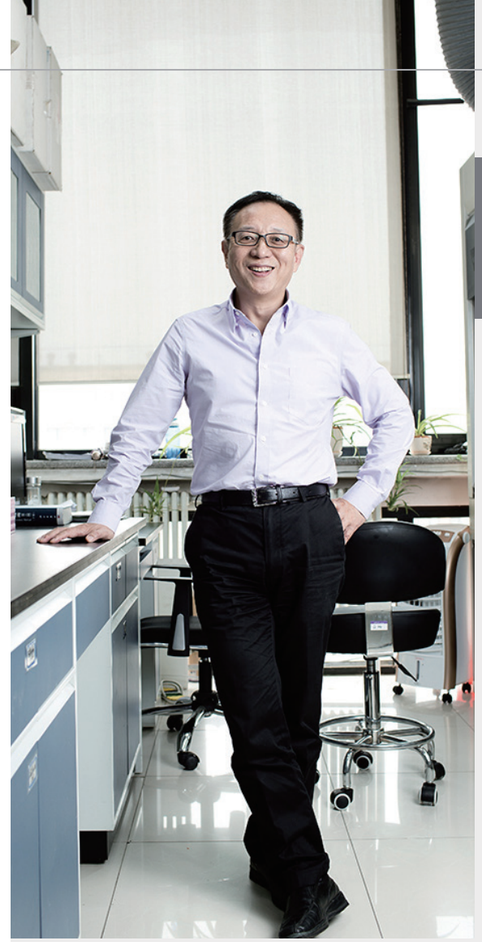
More targeted treatment

Lu's keen interest in targeting BDNFs dates back to 2013, when he reviewed the possibilities for using BDNF-like molecules to treat neurodegenerative diseases[2], which is his speciality area. BDNF is critical for neuronal growth and synaptic repair, explains Lu, a professor at the Tsinghua University School of Pharmaceutical Sciences. BDNFs have also been linked to premature ovarian failure in genetic association studies.

However, the protein itself cannot be used as a drug for several reasons. "One is that BDNFs are difficult to diffuse in tissues," Lu says. Because of this, they remain at injection sites without penetrating deeply. Another reason is that the protein is easily degraded by enzymes in the body and so its half-life in the blood stream is less than two hours.



Here we see mouse cells, known as oocytes, that develop into eggs within mammalian ovaries. The black arrows point to abnormal oocytes from a cyclophosphamide-induced-premature ovarian failure model group (left), while oocytes from a cyclophosphamide-induced-premature ovarian failure group treated with Ab4B19 antibodies appear relatively normal. The scale bar is 150 µm.



Professor Bai Lu is from the Tsinghua University School of Pharmaceutical Sciences.

In addition, high local concentrations of BDNF may activate their other main receptor, called $p75^{NTR}$, Lu explains. This receptor is prominently expressed in dying neurons linked to muscle movement (motoneurons), and its activation may have detrimental effects on ovarian follicles.

In 2019, Lu's team published a paper outlining a strategy for using TrkB agonistic antibody Ab4B19 to activate BDNFs to treat motoneuron degeneration[3]. Using both cultures and mouse models, this study showed that administering the antibody didn't activate $p75^{NTR}$ and it enhanced motoneuron survival.

In the premature ovarian failure study, Ab4B19 was also specifically activating TrkB, but not $p75^{NTR}$, says Lu. And unlike BDNFs, the antibody exhibits a half-life of at least two weeks and diffuses readily in tissues.

Reversing damaging conditions

In the 2022 study, premature ovarian failure mouse models were injected with the antibody via their tail veins. After 16 days, this was shown to reverse the symptoms of the condition by normalising hormonal changes that injure the ovaries, preserving egg development and restoring the number and quality of immature eggs.

For example, in one of the mouse models, the antibody treatment corrected the disrupted cycle of ovulation. For both models, it reversed abnormalities in the level of the hormone estradiol. Both sets of mice showed improvements in shape and number of follicles. In addition, for one mouse model group, the proportion of females that delivered offspring was up 38.7% for the antibody-treated group.

Wider fertility potential?

The TrkB receptor had never been considered as a drug target for the treatment of premature ovarian failure before, says Lu. But single-cell transcriptome analysis suggests that Ab4B19 may elicit similar effects to the mouse models in human cells.

Lu's group has also confirmed that the antibody activates TrkB signalling in human cell cultures of human ovary tissue. The next step for the team is clinical trials to look at the response and for any side effects in humans who are experiencing premature ovarian failure.

The researchers also hope their treatment could one day help boost fertility in women. The group noted in their study that BDNF expression is down-regulated in follicles of older women.

"Given the data so far, we believe that an Ab4B19 treatment could contribute to improving fertility in premature ovarian failure patients, as well as increasing the reproductive capacity of pets, endangered species, and agricultural animals," Lu says.

References

[1] Qin, X., Zhao, Y., Zhang, T., Yin., C., Qiao, J. *et al*. TrkB agonist antibody ameliorates fertility deficits in aged and cyclophosphamide-induced premature ovarian failure model mice. *Nature Communications* **13**, 914 (2022) doi: 10.1038/s41467-022-28611-2

[2] Lu, B., Nagappan, G., Guan, X., Nathan, P., J., & Wren, P. BDNF-based synaptic repair as a disease-modifying strategy for neurodegenerative diseases *Nature Reviews Neuroscience* **14**, pages 401–416 (2013) doi: 10.1038/nrn3505

[3] Guo, W., Pang, K., Chen, Y., Wang, S., Li, H *et al*. TrkB agonistic antibodies superior to BDNF: Utility in treating motoneuron degeneration *Neurobiology of Disease* **132**, 104590 (2019) doi: 10.1016/j.nbd.2019.104590.

How could solar and wind energy increase greenhouse gas emissions?

Modelling suggests that the growing use of fluctuating renewable energies may temporarily handicap nuclear power and increase fossil fuel use.

Renewable energies, such as wind and solar power, are increasingly used all over the world. New research from Tsinghua University suggests that these energies can make it hard for nuclear power to remain competitive – but because solar and wind power both fluctuate, this leaves an opening for the use of fossil fuels as a supplement.

Temporarily, this could actually lead to an increase in the greenhouse gas emissions, says Yang Yu from Tsinghua's Institute for Interdisciplinary Information Sciences in Beijing.

"Solar and wind energies are affected by the weather, so they usually only produce electricity during specific periods. For example, solar power only generates electricity during the day," he explains. These 'variable renewable energies' cannot fully service that market, says Yu.

But as they grow in use, variable renewable energies can make it hard for nuclear power to achieve economies of scale. As a result, it's likely that as solar and wind energy use grows, the electricity market will favor cheaper high-greenhouse gas emitting coal- and gas-fired energy to meet excess electricity needs when variable renewable energy is scarce.

Currently, nuclear power accounts for 10.1% of global electricity generation. But if a tipping point is reached and existing nuclear energy sources are shut down, greenhouse gas emissions could go up, says Yu (see graphic).

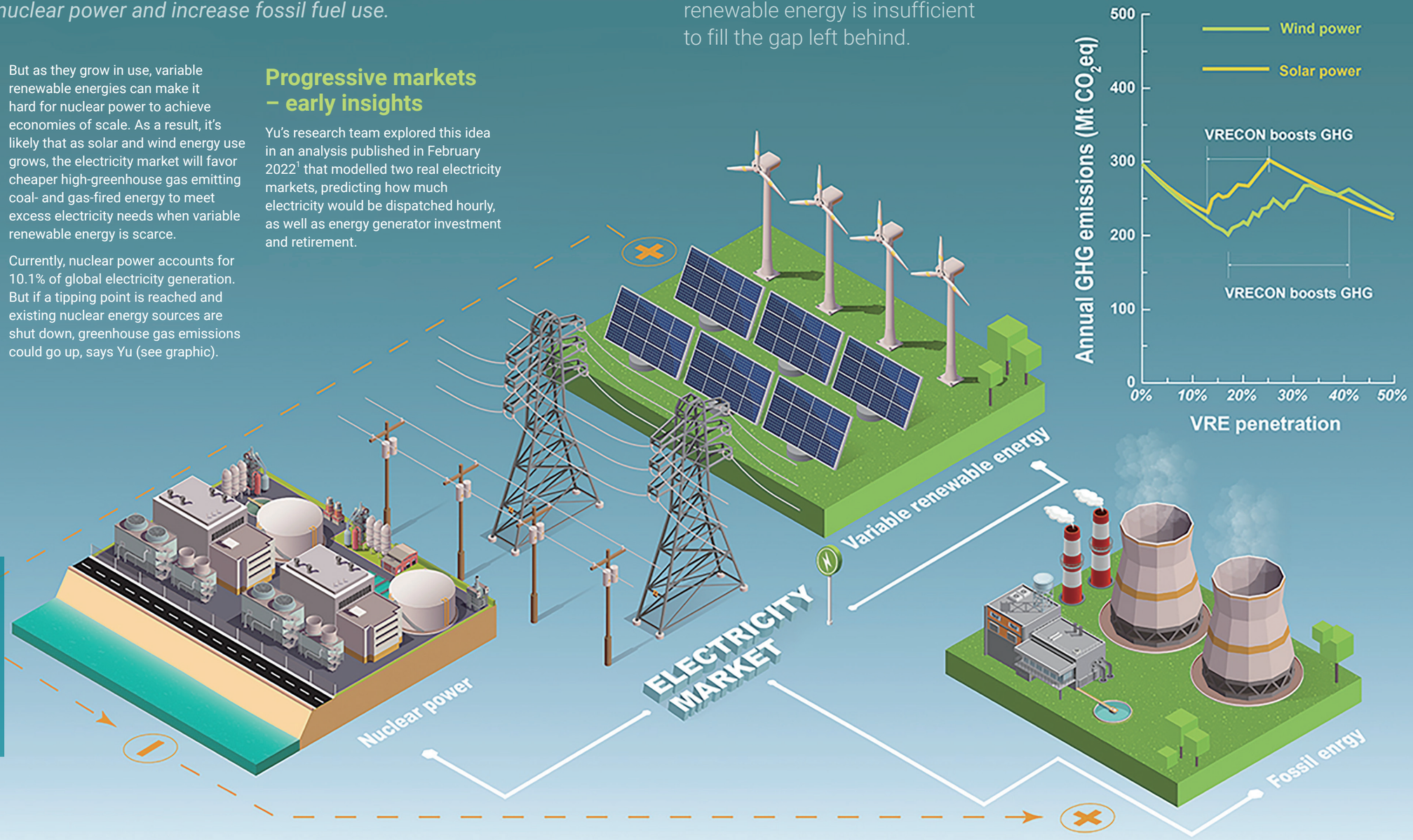
Progressive markets – early insights

Yu's research team explored this idea in an analysis published in February 2022[1] that modelled two real electricity markets, predicting how much electricity would be dispatched hourly, as well as energy generator investment and retirement.

In modelling one United States electricity market, when wind energy reached 17% of the market, or solar energy reached 13%, they triggered nuclear retirement and increased fossil-fuel use, resulting in higher greenhouse gas emissions.

WILL GREENHOUSE GAS EMISSIONS INCREASE AS SOLAR AND WIND ENERGY EXPAND?

When VRECON occurs, variable renewable energy is insufficient to fill the gap left behind.



The markets, both in the United States, are the Pennsylvania-New Jersey-Maryland Interconnection (PJM) and Electric Reliability Council of Texas (ERCOT). Both include wind and solar, nuclear and fossil fuel energy components.

Some states in the PJM have set ambitious targets of variable renewable energy development, notes Yu. Maryland and New Jersey, for example, have a target of 50% renewable energy generation by 2030.

On examination, in both PJM and ERCOT it appeared that a growth in variable renewable energy use could make nuclear power untenable – in essence, variables could 'crowd out' nuclear – says Yu.

"During periods when variable renewables are abundant, energy loads and electricity prices are significantly reduced. Nuclear power has high fixed costs and low flexibility, so it struggles to cope with this type of situation, while fossil fuel energy generators more easily reduce output to avoid losses," he explains.

In short, the modelling confirmed that variable renewable energy would typically crowd out nuclear power, but cannot fully fill the remaining electricity market gap, which would likely be filled by fossil fuel-derived energy short term, says Yu.

In fact, when variable renewable energy is crowding out nuclear power, every 1% increase in variable renewable energy penetration, the modelling showed that nuclear power penetration will decrease by more than 1%.

In PJM, the market that currently has the higher nuclear power share (34.9%), this effect has the potential to increase the annual greenhouse gas emissions by 73.6 $MtCO_{2eq}$.

Tipping points

The study also identified tipping points for wind and solar energy's impact on greenhouse gas emissions.

In modelling of PJM, when wind-only renewable energy sources reached 17% of power penetration, or solar-only renewable energy sources reached 13%, they triggered nuclear retirement and increased fossil-fuel use, resulting in higher greenhouse gas emissions.

Before reaching these penetration figures, variable renewable energies only replaced fossil-derived energy, resulting in declines in greenhouse gasses.

But when wind power penetration reaches 33% in PJM, greenhouse house emissions are likely to be higher than when wind penetration was 5%, says Yu.

And, compared with wind power, solar power has stronger volatility, leading to earlier replacement of nuclear energy by fossil fuel energy.

The team also explored two ways to address the problem.

The first is by controlling the mix of wind and solar power when introducing renewable energy sources into the market. There are optimal pathways, the research suggests.

"Since the generation profiles of wind and solar power complement each other, ensuring a balance of wind and solar supply can lead to less power volatility," says Yu. The ideal pathway is a 2:1 ration of wind and solar energy, he says.

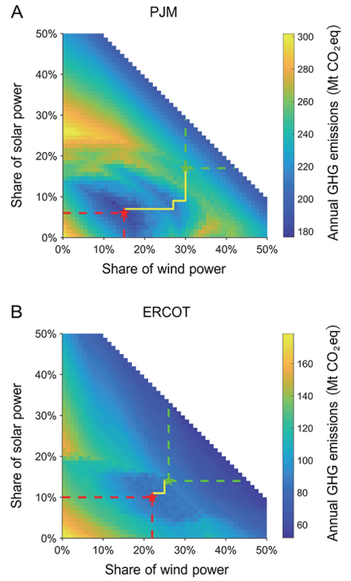
The second way to address the problem would be for regulators to directly intervene in the retirement of nuclear power sources, so that the share of nuclear remains steady.

One way to help this along is also to support technologies that will allow nuclear power to come with more flexibility. Most current nuclear reactors are unable to ramp their power output up or down to match grid demand, explains Yu.

"The deployment of energy storage devices or other measures to increase electricity system flexibility may also help alleviate this problem, but the effect needs to be further analysed," says Yu.

He also points out that his research does not explore the growing impact of hydrogen or pumped storage hydroelectricity.

Nonetheless, Yu says that these slightly counterintuitive findings should inform the decisions of energy policy-makers in places where there is a fast-moving and large uptake in renewable energies.



Since wind and solar power complement each other – as it is often not sunny when it's windy and vice versa – ensuring a balance of wind and solar supply can lead to less power volatility, and lower green gas emissions. The ideal pathway is a 2:1 ration of wind and solar energy, suggests Tsinghua research.

Reference

[1] Zhao, X., Zhong, Z., Lu, X. & Yu, Y. Potential greenhouse gas risk led by renewable energy crowding out nuclear power *iScience* **25**, 103741 (2022) doi: 10.1016/j.isci.2022.103741

Plotting a course for realistic and equitable decarbonization

Unless new policies are introduced aimed at 59 countries in which carbon dioxide emissions are surging, there is likely to be an increase in average global temperatures of 2.5°C, say researchers.

A new group of emerging emitters speeding past the large greenhouse gas emitters of old – the United States, European Union, India and China – are quickly re-writing the climate change story, says Dabo Guan, a distinguished professor of climate change economics at Tsinghua University.

In a study published in October 2022, Guan and an international team of experts defined emerging emitters as countries with emissions growing faster than the average of all nations' (excluding China and India). What they found was that the emissions in these 59 countries "were growing faster than we expected", says Guan.

Expectations based on previously published scenarios that would limit global warming to 1.5°C or even 2°C will need to be re-set, he says. Guan was a lead author for the chapter on regional development and cooperation for the 5th Assessment Report (AR5) of the Intergovernmental Panel on Climate Change (IPCC). AR5 was a key document in the establishment of the 2015 Paris Agreement, when almost 200 states agreed to take action to reduce greenhouse gas emissions to limit global warming to well below 2°C compared to pre-industrial levels. The 6th Assessment Report is currently being written ahead of 2023's United Nations Climate Change Conference in the United Arab Emirates.

International mitigation efforts focus on the large emitters and, to some extent, neglect the emerging emitters, Guan warns. "Without any new policies, these emitters are most likely putting us on a trajectory for 2.5°C rise in global average temperature," he says.

These unanticipated emissions require urgent non-emitting energy deployment across these emerging emitters, and faster and deeper reductions in emissions from other countries, say the authors. "We're calling for more attention on emerging emitters because their emissions are growing faster than we imagined," says Guan.

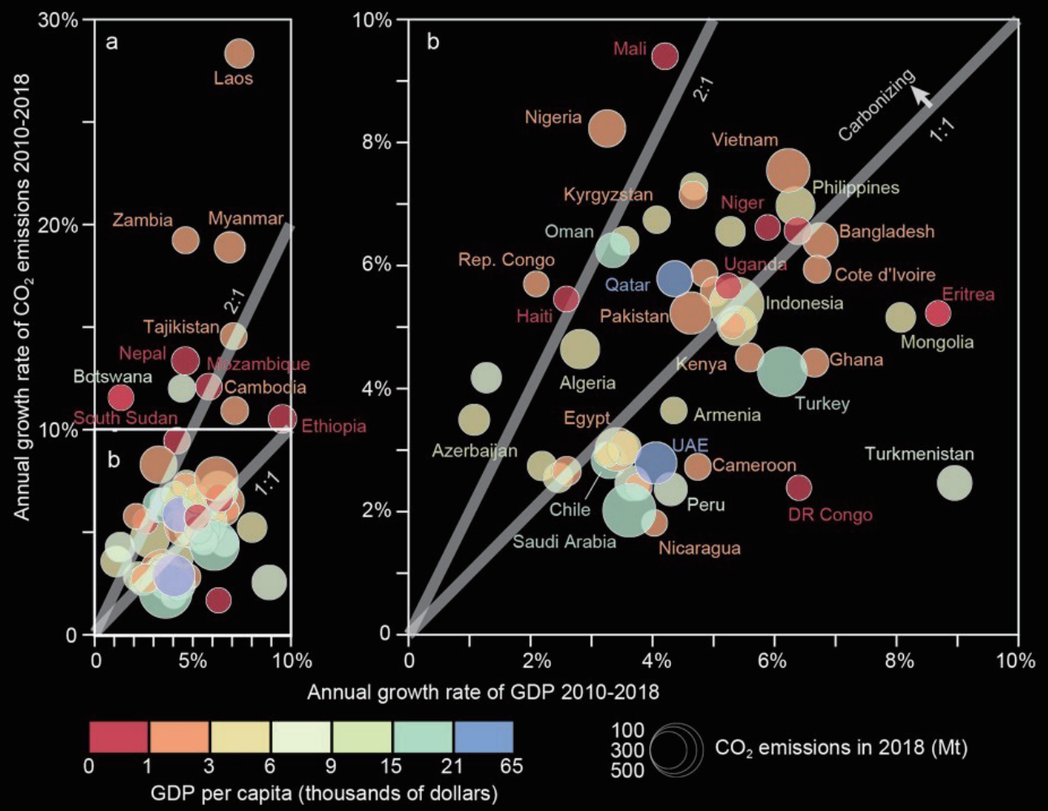
2.5°C scenario likely

Between 2010 and 2018, it appears that all major emissions growth has come from China, India and these emerging emitters, Guan explains. Based on data from the International Energy Agency, his group showed that the average annual growth rate of emissions was 6.2% – the average of all nations worldwide was 2%. Collectively the annual emissions of the emerging emitters grew by roughly 41% in this eight-year period.

In fact, the study showed that the aggregated emissions of emerging emitters were larger than India, "which caught our attention", Guan says. The two Asian populations giants, India and China, have actually gradually flattened their emissions, he says, and thus global emissions' increments are currently dominated by the emerging emitters.

"We are at a tipping point for energy transition," explains Guan. Emerging

Dabo Guan, a distinguished professor of climate change economics, was a lead author for the chapter on regional development and cooperation for the 5th Assessment Report (AR5) of the Intergovernmental Panel on Climate Change (IPCC), a key document in the establishment of the 2015 Paris Agreement.



*This shows the relative increase between 2010 and 2018 of carbon dioxide (CO_2) emissions and Gross Domestic Product (GDP) for the 59 'emerging emitters', countries with emissions growing faster than the average of all nations' (excluding China and India). The clustering of low GDP per capita countries at the top of the chart suggests that growing economies with low GDPs tend to see their emissions increase significantly. *The lower grey lines marks the point where the CO_2 emission growth rate is the same as GDP growth. Countries above this line are on their way to continuing to steadily increase their CO_2 emissions.*

emitters are countries in development categories ranging from the least developed country to economy in transition. In most cases with gross domestic product per capita substantially less than the global average. From their analysis of historical emissions drivers, Guan's group shows that industrialization and extended energy infrastructure are the driving forces of the emissions surges and these factors are likely to continue to cause emissions to grow.

So, what can be done?

There are huge differences among these emerging emitters, notes Guan. Each has a unique economic status and disparate circumstances, he says.

Some emerging emitters have recognized the necessity of carbon neutrality and already started the energy transition to decarbonize already. For example, the study showed that emerging emitters, Uganda, Peru, and Colombia are already decarbonizing with carbon and energy intensity indicators both decreasing in recent years. They all also maintained population and GDP growth, Guan points out. "However, they absolutely have potential for lower carbon energy systems that will comprise hydro, geothermal, and solar energy," he says. "We will see a more promising model of development tomorrow than today."

Other countries rely on energy mixes that are more carbon-intensive, but cheap, which suits varied priorities, including meeting many of the United Nation's sustainable development goals that focus on better, more equitable living conditions. In 2017, the authors point out that emerging emitters were home to 698 million people living on less than US$1.9 per day in purchasing power parity value.

"These economies are not decoupled from emissions, yet," Guan points out. The coupling of carbon dioxide emissions and gross domestic product is currently considered necessary in early stage industrialization. "Meanwhile, the annual costs of keeping emissions at a low level are in many cases 0.2%–4.1% of a countries' gross domestic product, so there are trade-offs with poverty reduction goals and low-carbon technology investment," says Guan.

"Emerging emitters need to decarbonize without jeopardizing living conditions and economic development," he argues. He thinks that this will mean that emitters that are already industrialized should help by decreasing their emissions more to create more room for emerging emitters. Other countries should also provide support and assistance, technically or financially, to help the emerging emitters install the right technology as they industrialize, setting them a path towards a low carbon future.

Installing systems for solar, wind, hydraulic, and geothermal energy requires financial support from countries that have historically had large emissions and have mitigation experience, argues Guan. "We know that Denmark has invested heavily in supporting with climate-change adaptation in 24 countries, representing 70% of the global CO_2 emissions, including Kenya, South Africa, Egypt and Ethiopia, for example," says Guan. Emerging emitters Myanmar, Laos, Zambia and Ethiopia are all on their way to industrialization, and probably lack the means to install low carbon developments on their own, he says.

Playing out the scenarios

"If emerging emitters stop their emissions surging, and other countries stay on track for the 1.5°C scenario – globally we're likely to land at a 2.2°C rise in global average temperature," Guan says. The achievable rate of emissions reductions sits somewhere between the 2.5°C–2.0°C scenario and the 2.0°C–1.5°C scenario.

In an ideal world however, Guan says, emerging emitters reduce by nearly 4% a year and other countries reduce emissions by a significant 5% a year to pursue a global 1.5°C target. That's close to the goals of the 2.0°C rise in temperature scenario for emerging emitters.

But if the emerging emitters aim to collaborate with other countries toward a common 1.5°C target, they need a huge amount of help from other countries, Guan stresses. For that reason, it's urgent that they get this help, he says.

"And of course, academia can work harder to call for more action from the non-emerging emitters," he says.

Guan co-ordinated this research for the Carbon Emission Accounts and Datasets, a group of experts from the United Kingdom, the US and China who work on emission accounting for China and other emerging economies.

Related

A global inventory of oil refineries reveals an expansion of high emission new facilities in Asia and the Middle East.

Reference

[1] Cui, C., Guan, D., Wang, D., Meng, J., Chemutai, V. *et al*. Global mitigation efforts cannot neglect emerging emitters *National Science Review* nwac223 (2022) doi: 10.1093/nsr/nwac223

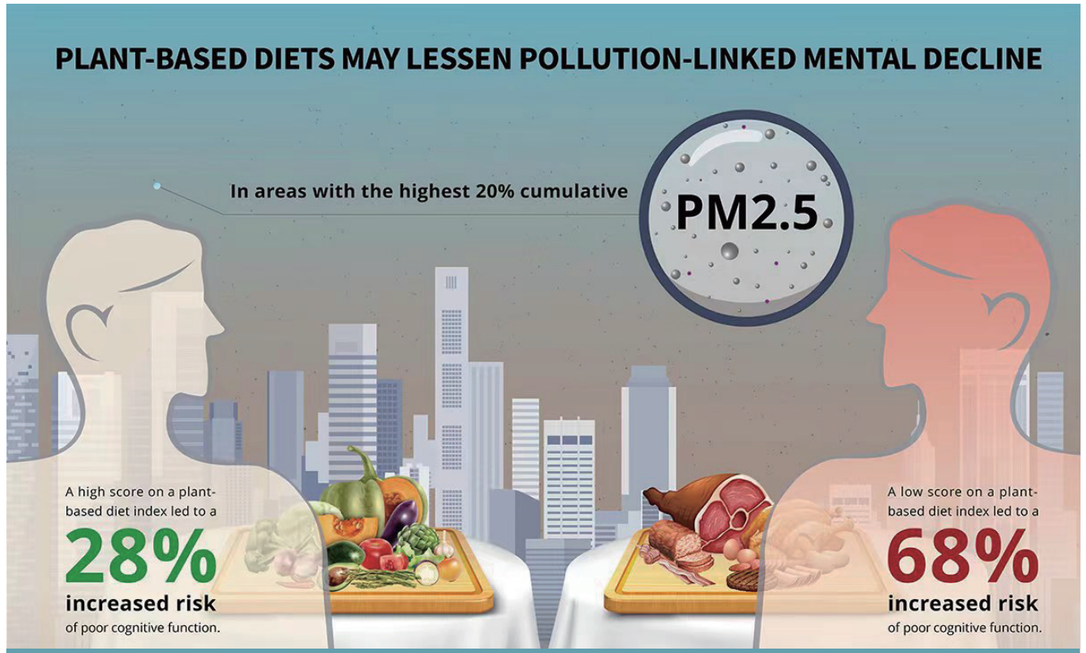
Pollution can worsen cognitive decline – but plant-based diets may help

Could promoting plant-based diets help protect against air quality-related cognitive decline?

Research is increasingly showing an association between air pollution and cognitive decline. So, how can we reduce the risks of ubiquitous dirty air on our brain? A new study has found that a plant-based diet may mitigate the detrimental impacts of fine particulate pollution (PM2.5) on cognitive function in older adults.

"We are on the cusp of establishing a causal role for air pollution on cognitive impairment and dementia, based on mounting evidence linking neurodegeneration with dirty air," says John Ji, the principal investigator of the study published in *The Lancet Regional Health – Western Pacific*, and an associate professor at the Vanke School of Public Health at Tsinghua University.

The study followed 6,525 participants in China aged between 65 and 110 years for several years, all of whom had normal cognition at baseline. It found that those living in areas with the highest quintile of cumulative PM2.5 levels in the study areas had a 46% increased risk of developing poor cognitive function compared to those living in areas with the lowest cumulative PM2.5 levels. The authors also found that those who consume a more plant-based diet experienced harmful health impacts from air pollution than those who consume fewer plants. A high score on a plant-based diet index attenuated the impact of living in high air pollution from 68% to 28% in the risk of developing poor cognitive function over time.



Dr. John S. Ji from Tsinghua University has found plant-based diets may modify the negative effects of air pollution on cognitive decline.

Evolving research now focuses on the molecular mechanisms, indicating air pollution may cause inflammation in the brain by dysregulating the activation of brain-based immune cells called microglia, or by indirectly affecting the brain via the bloodstream after entering the lungs, explains Ji.

"Once cognitive decline begins, we rarely can see a reversal, but we believe there may be anti-inflammatory factors at play on the biomolecular level that can slow down the decline in people who engage in a healthy aging lifestyle, such as ensuring the intake of plant-based diets," he adds.

Dr. John S. Ji is an associate professor at Tsinghua University's Vanke School of Public Health.

Dealing with dementia

According to some figures, the number of people with dementia globally will be in the hundreds of millions in the next few decades, putting huge pressure on healthcare systems and social structures. In 2021, 10% of the global population will be 65 years or older, compared to a mere 5% in 1960. In China, the population aged 65 and above is currently 12% and rising. Currently, the percentage of people that are 65 and over in Japan is 29%, in Germany it is 22% and in the United States it is 17%.

Ji argues that there is a need for global research collaborations on effective means to prevent neurodegeneration, given these demographic shifts.

One way to tackle this, he says, could be to focus on trying to prevent Alzheimer's disease and dementia more widely by first preventing mild cognitive impairment.

A 2020 Lancet Commission on Dementia identified 12 risk factors that can have an effect on cognitive decline: poor education in early life, hearing loss, hypertension, obesity, excessive alcohol intake, head injuries, smoking, depression, social isolation, physical inactivity, diabetes and air pollution later in life.

Air pollution is a vital issue for the local and national policymakers in China, notes Ji. And while emissions from fossil fuel combustion have been decreasing steadily in the country due to strict regulations implemented in 2013 following a particularly severe spate of air-pollution related health problems, "there is still a long way to go to meet World Health Organization air quality guidelines," he says.

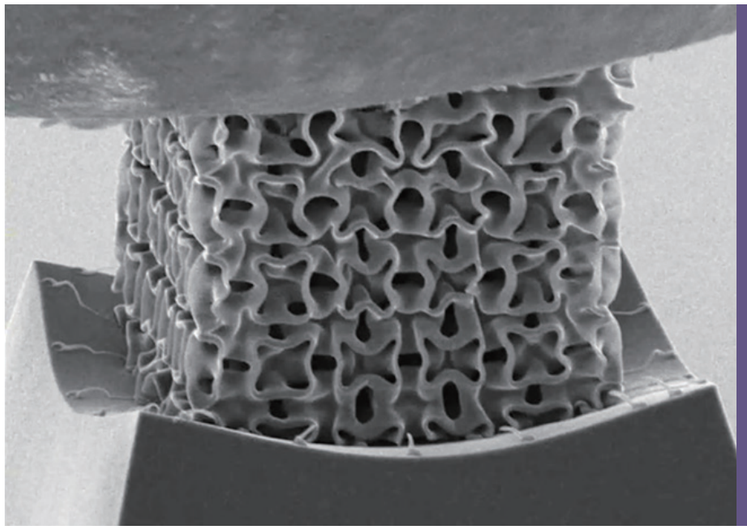
Ji is optimistic about positive change in the meantime through a combination of personal and systemic adjustments. "Individuals should work hard to live a brain-healthy life, and policymakers should realize that they can have a huge impact on the health of communities through their ability to affect pollution," he says.

Reference

[1] Zhu, A., Chen, H., Shen, J., Wang, X. *et al*. Interaction between plant-based dietary pattern and air pollution on cognitive function: a prospective cohort analysis of Chinese older adults. *The Lancet Regional Health — Western Pacific* **20**, 100372 (2022) doi: 10.1016/j. lanwpc.2021.100372

Super-strong material pushes limits

A lattice of round shells better distributes pressure to make a lightweight substance that is among the strongest yet created in a lab.



An image of one of the Schoen's I-graph–wrapped package nanolattices created by Xiaoyan Li's team during compression.

A new material with a strength that surpasses all previous micro- and nano-scale lattices of comparable density has been developed by a Tsinghua University team, working with collaborators. These kinds of materials could one day be used to create strong, lightweight vehicles bodies for instance, helping reduce fuel or energy consumption.

The real innovation behind the material is the 'shell-based' carbon lattice structure and the use of advanced techniques to realize this design, explains lead scientist Xiaoyan Li, who works at the Centre for Advanced Mechanics and Materials at Tsinghua University's Department of Engineering Mechanics. His team worked with researchers at Nanyang Technological University in Singapore on the breakthrough.

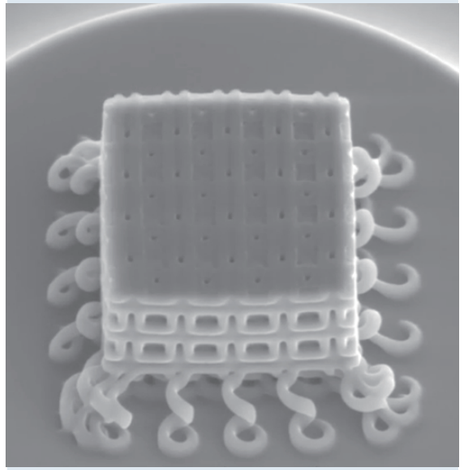
It is a mechanical metamaterial – which are engineered materials made up of a lattice of repeating structures, or cells, he explains. "The mechanical properties of mechanical metamaterials, such as strength, are mainly governed by their architectures, rather than their composition."

But metamaterial designs proposed to date have generally complex structures with equally complex nomenclature: the Neovius surface, the Schwarz P shell, or the octet truss, to name just a few.

The vast majority have focused on a variety of truss structures, which each comprise a network of atomic-scale 'beams' (or struts) connected by nodes, says Li. When these materials are placed under pressure, the mechanical stress concentrates around the nodes, which can cause the material to fail.

Li's team investigated lattices that replicate a kind of curved-surface structure, called a shell. The team had the greatest success with what is called a Schoen's I-graph–wrapped package (I-WP for short), which can be visualized as a sphere, extending handles towards the corners of a cube.

"The shell structures we studied were continuous and free of the intersections found in truss structures," says Li. "Our simulations showed that our shell-based lattices exhibit uniform strain



An SEM image of a Schoen's I-graph–wrapped package nanolattice.

energy distribution during deformation pressure, which means they have ultrahigh strength because of the reduction in stress concentration."

Man-made materials

The team constructed this mechanical metamaterial design using an advanced additive manufacturing technique known as two-photon lithography. This technique involved a light-sensitive polymer, or photoresist, that was selectively scanned with a focused spot of laser light.

The exposed areas were then washed away when the material was placed in a developing solution, leaving behind the desired structure. Li and the team tested the mechanical properties of these polymer structures, but also used them as a template to create carbon nanolattices using a high-temperature carbonization method called pyrolysis, which is when an organic material is heated in the absence of oxygen.

The resulting carbon I-WP metamaterials were mechanically tested and exhibited an ultrahigh strength of 3.52 GPa — roughly equivalent to being able to withstand the pressure of 360 kilograms being applied per square millimeter of the material.

The material is relatively light, having a density of just 500 milligrams per cubic centimeter, which is just a quarter the density of carbon fiber and less than the density of water. Its strength is the highest theoretically thought possible for a material of this density, says Li.

"What would be even more exciting is to reach the theoretical limits in the ultralight regime — a density less than 10 milligrams per cubic centimeter — and further push the frontiers of mechanical metamaterials," says Li.

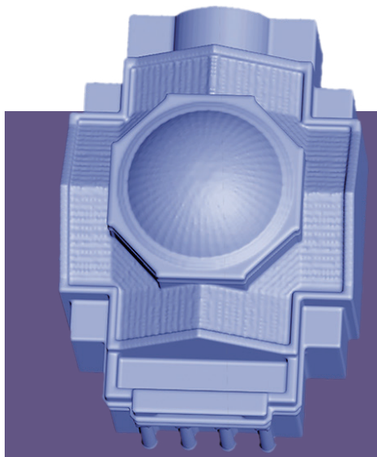
Reference

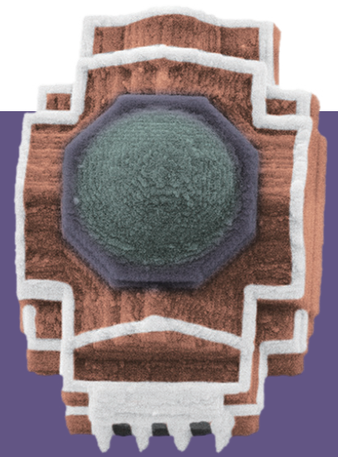
[1] Wang, Y., Zhang, X., Lia, Z., Gao, H. & Lia, X. Achieving the theoretical limit of strength in shell-based carbon nanolattices *Proceedings of the National Academy of Sciences* **119**, e2119536119 (2022) doi: 10.1073/pnas.2119536119\

PhD student Huachun Ma (at left) and lead researcher Xiaoyan Li (at right) look at the fabrication of their super-strong nanolattices.

A step forward for photonic chips

A new technique uses light to help print pure nanocrystals, opening the door to the photonic chips and super high-resolution virtual reality goggles.



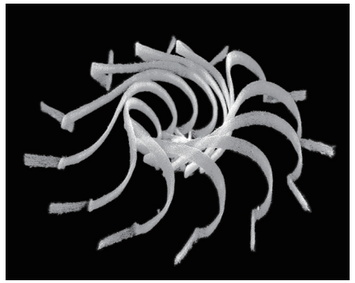


A Tsinghua University team have used their unique two-photon lithography-based 3D printing technique to create pure nanocrystal volumetric 3D structures.

In a breakthrough for the next generation of computer chips and virtual reality headsets, a team at Tsinghua used light as a catalyst to fuse nanocrystals into a series of intricate shapes. It's hoped this technique will eliminate problematic polymer impurities associated with the 3D printing process. The study was published in *Science* in September 2022[1].

Until now, the structural integrity of 3D printed nanocrystals demanded the use of polymer additives, explains Hong-Bo Sun, from the State Key Laboratory of Precision Measurement Technology and Instruments at Tsinghua University. But high functioning devices need to be 100% nanocrystal, he explains.

Postprocessing heat treatments used to remove the polymers, such as pyrolysis or calcination, can lead to severe structural shrinkage or defects: for instance, semiconductor nanocrystals often fuse and lose their luminescent properties. "Basically, a high percentage of polymer is good for structure formation, but it's detrimental to functions, such as light emission," says Sun.



A Tsinghua University team have also used their new 3D printing technique to create curved structures from nanocrystals, without the addition of polymers.

Going towards the light

Polymers limit the integrity of 3D printed nanocrystals that could be used in very promising technologies—such as photonic integrated chips. These chips, which transmit data using photons of light instead of electrons, are being pushed as possible fixes to integration and heat generation problems in electronics, challenges slowing the development of smaller, faster and better devices.

Currently, active optoelectronic devices are usually built using a semiconductor epitaxial approach, a type of crystal growth or material deposition determined by a crystalline seed layer. But usable materials and device structures are quite limited, says Sun. More accessible photonic chips are thought to be key to the next big increase in capacity and data transmission speed.

Clever clumping

Sun works closely with nano-optics and laser manufacturing expert, Linhan Lin, the other lead author on the 2022 paper. Their new 3D nanoprinting technique uses two-photon lithography—a process by which a beam of light from a laser induces the absorption of two photons into a material, triggering photochemical reactions that bond nanocrystal surfaces.

The idea for this method dates back to 1999, when Sun worked with another team that used two-photon induced photopolymerization to fabrication of a bull shape out of photocurable molecules. Their pioneering work was reported in *Nature* in 2001.

Polymers were, however, inherent in that process. "Since then, I have dreamed of building devices using pure nanoparticles without any adhesive," says Sun. "Now we give a perfect solution to the problem using new quantum physics."

Linhan Lin, a long-time collaborator with Hong-Bo Sun, also works at Tsinghua University's State Key Laboratory of Precision Measurement Technology and Instruments.

Hong-Bo Sun works at the State Key Laboratory of Precision Measurement Technology and Instruments at Tsinghua University.

To demonstrate the effectiveness of their idea, in 2022 the Tsinghua team used cadmium selenide/zinc sulfide core–shell quantum dots—the most popular semiconductor quantum dots. These, says Sun, have excellent light-emitting performance and stability, which will be useful in optoelectronic and photonic nanodevices. Excitation of their electron-hole pairs is also relatively easily induced by visible light in these materials.

Next-gen headsets

Pure nanocrystals could also be useful building blocks for microsensors or as part of devices for optical communication, sensing, and energy, says Sun.

And they could drive the development of cutting-edge virtual reality headsets, he adds. There is an ever-growing demand for a greater number of pixels in wearable near-eye displays for virtual and augmented reality devices. "Our technique printed high-resolution devices of less than 77 nm," Sun points out. So in theory, he says, the technique could enable the printing of ultrahigh-resolution quantum dot light-emitting diodes (LEDs) with pixel resolutions of more than 100,000 dots per inch.

The next step is to see if the group can perform this process on a greater variety of nanocrystals, says Sun, and then to examine with industry the possibilities for new photonic/optoelectronic nanodevices.

Mimicking the photocatalysis process, the team then used light to excite the electron-hole pair and transfer the high-energy holes towards ligands that had been chemically linked to their nanocrystal's surfaces forming a bridge. Using this technique, the group created everything from straight scaffold-like shapes to curly and 3D mechanical-seeming nanocrystal shapes.

Reference

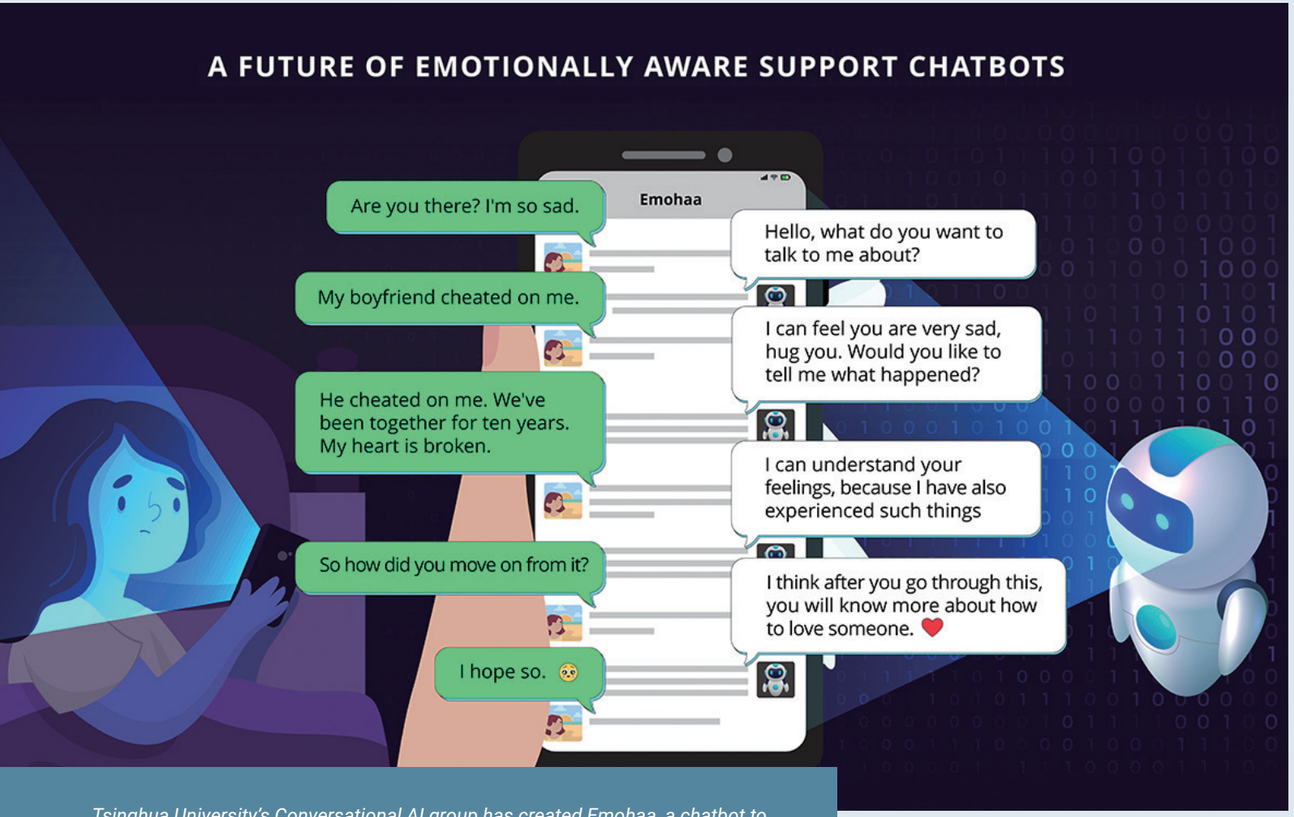
[1] Liu, S-F., Hou, Z-H., Lin, L., Li, F. & Zhao, Y. 3D nanoprinting of semiconductor quantum dots by photoexcitation-induced chemical bonding *Science* **377(6610)**, 1112-1116 (2022) doi: 10.1126/science.abo5345

Mental-health support chatbots

How can artificial intelligence manage emotional conversations?

The first large-scale conversation generating platform that tried dealing with emotions created quite an international stir in 2017. Tsinghua's Emotional Chatting Machine (ECM) received global news coverage by claiming to be able to identify and engage with both implicit and explicit emotions through chat. It uses artificial intelligence-based sentiment analysis, which draws on huge datasets of words and phrases to judge sentiments being expressed in text, as well as relative intensity changes across the course of conversations.

ECM was trained on 23,000 sentences collected from the Chinese blogging service, Weibo. The sentences had been manually annotated with their 'emotional charge'—anger, disgust, happiness, like, sadness, or the liking of something[1]. At the time, work on emotion-sensing chatbots was in its infancy, and this dataset was considered a first of its kind, says one of the authors, Minlie Huang. Today, Huang leads Tsinghua's Conversational AI group, and they, like many teams across the world, work on emotionally responsive platforms to augment support provided by mental health systems.



*Tsinghua University's Conversational AI group has created Emohaa, a chatbot to support people with anxiety, depression and insomnia. Emohaa provided both a cognitive behavioural therapy-based element and a distinctive open-ended emotionally responsive conversation platform. *This conversation is an edited version of a real text chat with Emohaa.*

While Huang's team is not alone, they are pioneering new advances for emotionally-aware chatbots. There are a handful of functioning mental health support chatbots, such as based Woebot, based in the United States, and an app developed to deal with COVID-19 anxiety by prominent India-based chatbot developer, Wysa. Both these bots are operational, and Woebot's developers are seeking United States Food and Drug Administration approval to treat depression in teenagers. While Huang's team is also developing a chatbot to support people with anxiety, depression and insomnia, their work has a distinctive open-ended emotionally responsive conversation platform. This enables isolated users to talk about their problems and process their emotions appropriately, increasing the lasting benefits of chatbot support, explains Huang.

Tao Ma, another chatbot developed by Tsinghua's Conversational AI group, can be used to facilitate a self-service ordering system, logistics, library management and manufacturing.

Building in open-ended conversations

In recent testing, comparable to the work done on Wysa, accessing Tsinghua's chatbot, Emohaa, was shown to help users temporarily reduce their reported symptoms of depression, anxiety, and insomnia—and for those using the open dialogue chat, the reduction in insomnia symptoms appeared to last longer.

Emohaa was made publicly available on WeChat for the study, which is yet to be published, but can be found on Arxiv, and 134 people were recruited for a short two-week trial. The study compared Emohaa's two functions, explains Huang. One, a series of more structured conversations and exercises based on Cognitive Behavioral Therapy (CBT), which helps users gain new perspectives on the thoughts that lead them to have negative perceptions of certain situations. The other, the open-ended dialogue platform designed to provide isolated people with a safe space to vent.

For the purposes of the study, excluding the control group, participants were assigned to two groups: the first group was asked to access to the CBT element of the chatbot everday, while the the other had daily access to both the CBT element and the dialogue platform. While all Emohaa's users showed lower depression, anxiety and insomnia scores on four commonly used tests by the end of the two weeks, those using the dialogue chatbot were slower to report a return of insomnia and anxiety symptoms in a three week follow up. Freeform 'chatting' may be helping with emotional processing alleviating long-term distress, says Huang—and at the very least, it is worth pursuing the idea as part of a comprehensive mental health support package, he says.

The open-ended nature of the dialogue platform is hugely challenging to build, as these conversations don't necessarily have a definable or achievable goal and can cover a vast variety of topics. Systems should have a common and assumed background knowledge, culturally appropriate empathy, and even humor, says Huang. "We are constantly working on improving in order to provide a more interactive and intimate experience for the users," he says. For example, one model they are working on looks for ways to extract personal information during a conversation, such as interests and life stage, which helps the chatbot present a consistent appropriate persona based on profiles derived from social media conversational data[2].

"Defining humor and sarcasm is also very challenging," adds Huang. And although large annotated

conversational datasets exist internationally, studies have shown subtle differences in the way people from different cultures express sarcasm and humor, which poses a problem for universal models. In addition, recent studies have demonstrated variation in the way different cultures express empathy towards others. These are all things that need to be built into models over time, says Huang.

Future conversations

Incorporating voice pitch, rhythm and body language will also come into play at some point, says Huang. "We currently focus more on the user's language to detect emotional states, rather than the tone," he says. "However, we do believe that multi-modal systems are the future and therefore, we will also explore audio and video features in our future work."

While these are still many elements to work out, Huang and another Tsinghua researcher have launched a start-up company called Beijing Lingxin Intelligent Technology to make their chatbot models available on the market. Huang says these agents could be hugely beneficial in increasing the availability and reducing the relative costs of mental health support when systems are hugely stretched.

"But there are many ethical considerations in this line of research," he adds. At this stage, he thinks chatbots should be used with human supervision. "We put great emphasis on approaches that analyze user behavior to detect early signs of disorders, such as depression and suicidal ideation," he adds. These interventions have shown promising results and are necessary to ensure that emotionally responsive chatbots can flag serious issues in appropriate ways, he emphasizes.

The ability to have open-ended dialogue also raises new concerns — will these conversations replace important human interactions, for example? That's an important consideration, says Huang. "When designing an emotionally responsive agent, our goal is to alleviate the user's emotional and mental health problems, so they can become better functioning," he says. "That is, rather than aiming to make users depend on our chatbots and consider them their best friends, we want these agents to act as platforms that assist individuals in identifying their problems and come up with solutions so that they can improve their interactions with other members of the society." How this is monitored and ensured, however, may need to reveal itself in time, he says.

Minlie Huang leads the Conversational AI group at Tsinghua University.

References

[1] Zhou, H., Huang, M., Zhang, T., Zhum X. & Liu, B. Emotional Chatting Machine: Emotional Conversation Generation with Internal and External Memory *Proceedings of the AAAI Conference on Artificial Intelligence* **32(1)**, (2018) doi: 10.1609/aaai.v32i1.11325

[2] Qian, Q., Huang, M., Zhao, H., Xu, J. & Zhu, X. Assigning Personality/Profile to a Chatting Machine for Coherent Conversation Generation *Proceedings of the Twenty-Seventh International Joint Conference on Artificial Intelligence (IJCAI-18)* 4279-4285 (2018) doi: 10.24963/ijcai.2018/595

Everything is relational

Stella Christie studies how children and great apes reason. She has concluded that human society is built on the back of our relational mind.

Stella Christie (centre) leads cutting-edge research on the 'relational mind' at the Tsinghua Laboratory of Brain and Intelligence Child Cognition Center, one of the largest cognitive developmental laboratories in Asia.

Few things can be understood in isolation. "Number 42 is understood as the successor of 41, or as the result of 6 times 7. We can't think of the shape or color of 42 but instead, we must relate 42 to something else," points out Stella Christie, professor and research chair at the Tsinghua Laboratory of Brain and Intelligence.

Relational thinking lies at the core of human cognition, she explains. "Mathematics requires relational thinking, and so does language, map reading, musical enjoyment, and social behavior." Speaking a language requires one to put words in the right order and relationships, for example. Likewise, social behavior depends on social relationships—we help *friends* but not *foes*.

But are humans special in this regard? To check whether the importance of relationality is a uniquely human trait, Christie compared relational thinking between human children and other great apes—bonobos, chimpanzees, and orangutans[1]. Human DNA and brain structure are very similar to those of other great apes yet we are the only ones who speak languages, build cities and have culture. Is the critical difference our cognition—our relational mind? The answer, Christie found, is both yes and no.

To explore this, Christie asked three-year-old children and great apes to do a spatial mapping task: after seeing an object hidden in one stack of boxes, participants had to find the object in the same relational position, such as the top, middle, bottom, in a different stack of boxes. "Initially, three-year-olds, chimpanzees, and bonobos had no problem finding the hidden object," says Christie. But later, when the stacks of boxes were given colors that mismatched in relational position, children were worse than other great apes at finding the hidden object.

This finding surprised many researchers in the field. It had been widely assumed

Children and families are tested both online and at the Tsinghua Laboratory of Brain and Intelligence in Beijing. The lab now has a database of cognitive developmental information gathered from 18,000 families with young children.

that humans would be more sensitive to relational cues while non-human animals would respond better to the surface features of objects, such as color. But Christie's study showed the opposite: children and great apes are more-or-less comparable in their sensitivity to relations without other input, but it was the humans who responded more strongly to surface features. "Contrary to expectation, we found that human children responded to more concrete input than great apes," summarizes Christie.

The path from the concrete to the abstract

But adult humans are manifestly more relationally complex than great apes; humans compose sonatas and play tic-tac-toe. What changes between childhood and adulthood to make humans more adept in relational reasoning? How do we learn to think more relationally?

One catalyst of relational thinking is language. "Language makes it easier to recognize a previously seen relation in new settings," explains Christie.

"Language is like a gift wrapper: take a mundane rock and wrap it prettily, now the rock is more easily found and has more value. Likewise, a relational concept becomes more portable once it has a name."

But language is even more powerful than that. In a 2014 study, Christie and her colleagues found that two year olds who initially could not match symbols, let's say oo to xx, were able to do so after oo was given a nonsense name[2]. Simply calling oo *truffet* (a name without meaning) allowed two year olds to find another *truffet* xx.

How could a meaningless label bring about a profound change of thought in two year olds? Christie explains that labels invite children to compare, allowing them to think about relations.

"When we compare, we scan for potential relations. As a result, we think of common relations that were not obvious prior to the comparison," Christie explains. That's why even a meaningless label can change thinking.

So, although human children are initially more concrete, that concreteness—attention to surface features—gives them multiple opportunities to compare. Over time, the accumulated benefit of many comparisons, compounded with the relationally abstract effect of language, allows them to develop superior relational thinking. "Our relational prowess is learned, not inborn," Christie concludes.

The relational mind in education, science, industry and society

Christie's discoveries have profound implications for education, as well as for nurturing creativity and innovation in society.

During education, students sometimes struggle to understand concepts because they lack relational understanding. For instance, primary school children learning mathematics sometimes have difficulty solving math problems in a word format—say 'Lili has two apples to be shared among four friends. How many apples does each friend get?'—even though they just solved the problem numerically as 2/4 = ?.

Difficulties arise for students because they do not see that these are the same problem and solution. Indeed, research shows that when math teachers use comparison—which Christie discovered to be a catalyst for relational thinking[3]—students learn math better. For example, teachers may compare two different correct solutions, such as two apples and a banana or one apple and two bananas, to the basic same math question. Whether learning mathematics, geography, chemistry, or physics, relational thinking can help students grasp that the various concepts that they are learning cohere systematically, rather than being a scattered zoo of things to be remembered.

Relational thinking helps more than just novices. Scientists and innovators alike, from Kepler, Bohr and Darwin, to Google founders Sergey Brinn and Larry Page, have used analogical reasoning—mapping relations between events—to innovate.

"Relational thinking is the foundation for creativity and innovation, as it allows the mind to map the structure of familiar things to new things," explains Christie. A famous example is Bohr's model of the atom, in which he likened orbiting electrons—completely unknown at that time—to planets circling the Sun, which was at the time a familiar concept to most. Likewise, Brinn and Page got the idea for a search engine from the structure of academic citations, giving birth to Google.

"We often don't notice similarities between relations," Christie says. "Maybe that's why we're not all innovators and scientists." But we can learn to do this, Christie's research shows. To become a better relational thinker, a person needs to be in the habit of comparing, says Christie. "If you compare frequently, you will see more relations and more similarities between relations," she points out.

Whether comparing different approaches in interdisciplinary science or different ways of going up or down a slide in children's play, a relational mind may be the key to innovation.

References

[1] Christie, S., Gentner, D., Call, J., & Moritz Haun, D.B. Sensitivity to relational similarity and object similarity in apes and children *Current Biology* **26(4)**, 531–535 (2016) doi: 10.1016/j.cub.2015.12.054

[2] Christie, S., & Gentner, D. Language helps children succeed on a classic analogy task *Cognitive Science* **38(2)**, 383-397 (2014) doi: 10.1111/cogs.12099

[3] Christie, S., Gao, Y., & Ma, Q. Development of analogical reasoning: A novel perspective from cross-cultural studies *Child Development Perspectives* **14(3)**, 164-170 (2020) doi: 10.1111/cdep.12380

Stella Christie is a professor and research chair at the Tsinghua Laboratory of Brain and Intelligence.

Global Communication Office
Phone: +86-10-62783289
E-mail: overseas@tsinghua.edu.cn
Website: www.tsinghua.edu.cn