to be included in the vaccine formulation[3]. Many adjuvants included in injectable vaccines are unsuitable for respiratory immunization. Ye and colleagues included a non-toxic bacterial protein called CTB as an adjuvant. CTB has been used safely in an orally administered human cholera vaccine[3], but it will be necessary to find out whether it is safe and effective when inhaled by humans. After intranasal delivery, CTB-adjuvanted vaccine is observed in the olfactory bulb in mice[6]. Some human participants in clinical trials developed a transient type of facial paralysis (Bell's palsy) after receiving intranasal vaccines containing a different type of bacterial toxin (LKT63) as an adjuvant[3].

It is time to develop next-generation vaccines that can be delivered to the respiratory tract, not only against SARS-CoV-2 but also against other infections. Moving promising candidates such as the one developed by Ye *et al.* from the bench into clinical trials will be a crucial step forwards. So far, few clinical COVID-19 vaccine trials have assessed the induction of mucosal immunity in the LRT after respiratory immunization. Future trials will need to fill this gap by using bronchoscopy to sample immune cells from the LRT and to search for biomarkers in the bloodstream that correlate with respiratory mucosal immunity. Furthermore, the delivery device, scalability and affordability of inhalable, protein-based nanoparticle vaccines also needs to be considered.

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Forum: Technology

2D materials ratchet up biorealism in computing

A transistor made from atomically thin materials mimics the way in which connections between neurons are strengthened by activity. Two perspectives reveal why physicists and neuroscientists share equal enthusiasm for this feat of engineering. **See p.551**

The paper in brief

- **The brain offers ample inspiration for computer engineers, but such 'neuromorphic' devices can be disadvantaged by huge power consumption, limited endurance and considerable variability.**
- **One of the challenges associated with optimizing these devices involves ascertaining which brain characteristics to emulate.**
- **On page 551, Yan *et al.*[1] report a type of synaptic transistor — a device named after its similarities to neural connections known as synapses — that maximizes performance through a ratcheting mechanism that is reminiscent of how neurons strengthen their synapses.**
- **The transistor could enable energy-efficient artificial-intelligence algorithms, and reproduce some of the many sophisticated behaviours of the brain.**

Frank H. L. Koppens

A new twist on synaptic transistors

At the heart of Yan and colleagues' innovation lies the unusual behaviour of electrons that arises when materials of single-atom thickness are stacked together and then twisted relative to each other. The materials in question are bilayer graphene, which comprises two stacked layers of carbon atoms, sandwiched together by two layers of the dielectric material hexagonal boron nitride (hBN)[2]. Both of these materials have hexagonal crystal structures, but the spacing between their atoms differs slightly. The overlapping hexagonal patterns create regions of constructive and destructive interference, resulting in a larger-scale pattern known as a moiré lattice.

> **"The device can be tuned, a feature that shares similarities with behaviour observed in biological neural networks."**

The moiré pattern modifies how electrons are distributed in bilayer graphene: it localizes them periodically throughout the crystal lattice (Fig. 1a). Electrons in the top layer of graphene are affected more by this periodic modulation because the crystal structure of this layer is aligned with that of the hBN above it, and this essentially makes the electrons immobile. By contrast, the hBN below the bottom graphene layer is rotated out of alignment with the graphene, resulting in a weaker electronic modulation[3]. The electrons in this layer are therefore mobile, and they contribute to the current flow.

This asymmetry between layers makes the transistor function like a kind of ratchet, controlling the flow of mobile electrons and regulating the device's electrical conductance, which is analogous to synaptic strength. The ratchet is controlled by two 'gates' above and below the structure, which regulate the number of electrons in the graphene system. When a voltage pulse is applied to the top gate, the initial rise in voltage adds immobile electrons to the top graphene layer. And when the electron energy levels in this layer are filled, mobile electrons are added to the bottom graphene layer. A subsequent decrease in voltage removes electrons from the top graphene layer, however the mobile electrons in the bottom layer remain. In this way, the voltage pulse changes the conductance in a manner that is reminiscent of the strengthening of a synaptic connection.

What sets Yan and co-worker's moiré device apart from existing synaptic transistors is that it can be easily tuned, a feature that shares

similarities with synaptic behaviour observed in biological neural networks. This makes the transistor ideally suited to advanced artificial intelligence (AI) applications, particularly those involving 'compute-in-memory' designs that integrate processing circuitry directly into the memory array, to maximize energy efficiency. It could also allow information to be processed on devices located at the edge of a network, rather than in a centralized data centre, thereby enhancing the security and privacy of data.

Although the authors' transistor represents an important leap forwards, it is not without its limitations. For instance, stacking the ultrathin materials requires sophisticated fabrication processes, which makes it challenging to scale up the technology for widespread industrial use. On a positive note, there are already methods for growing large-area bilayer graphene[4] and hBN[5], up to the typical 200- or 300-millimetre sizes used in the silicon industry. This sets the stage for an ambitious, yet timely, endeavour: the fully automated robotic assembly of large-area moiré materials.

If accomplished, this would make Yan and colleagues' device easier to fabricate, and unlock other moiré-material innovations, such as quantum sensors, non-volatile computer memories and energy-storage devices. It would also bring us closer to integrating moiré synaptic transistors into larger, more complex neural networks — a crucial step towards realizing the full potential of these devices in real-world applications.

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James B. Aimone & Frances S. Chance

Capturing the brain's functionality

Yan and co-workers' advance addresses a long-standing challenge at the intersection of neuroscience and computing: identifying which biophysical features of the immensely complicated brain are necessary for achieving functional neuromorphic computing, and which can be ignored. The authors have succeeded in emulating a characteristic of the brain that is particularly difficult to realize — its synaptic plasticity, which describes neurons' ability to control the strength of their synaptic connections.

Existing synaptic transistors can be connected together in grid-like architectures that mimic neural networks. But dynamically reprogramming most of these devices remains unreliable or expensive, whereas the brain's synapses can adapt reliably and robustly over time. Moreover, even if biological mechanisms of synaptic plasticity can be implemented in an artificial system, it remains unclear how to leverage these mechanisms to realize algorithms that can learn like biological systems do.

The authors' moiré synaptic transistor brings the flexibility and control necessary for brain-like synaptic learning by providing a powerful way to tune its electrical conductance — a proxy for synaptic strength. The device's asymmetric charge-transfer mechanism is reminiscent of processes known as long-term potentiation and long-term depression, in which pulsed electrical stimulation has the effect of strengthening a synapse (or weakening it, in the case of depression). The ratcheting of charge carriers can be considered analogous to the enrichment of protein complexes, known as AMPA receptors, at synapses during long-term potentiation and long-term depression[6] (Fig. 1b).

Inspired by observed behaviours in biological synapses, Yan *et al.* showed that their device could be used to train neuromorphic circuits in a more 'brain-like' way than has previously been achieved with artificial synapse devices. Although the two gates in the moiré synaptic transistor could be used in a simple manner to fine-tune synaptic strength (or electrical conductance) directly, in biology, the control of synaptic learning is more nuanced. The authors recognized that aspects of this finer control could also be realized in their device.

Specifically, Yan *et al.* were able to tune the top and bottom gate voltages to make their moiré synaptic transistor exhibit input-specific adaptation, which is a phenomenon that allows a neuron to control its synaptic learning rates in response to averaged input. This mechanism is used when the eye is deprived (of adequate lighting, for example) to help the brain recall a stored pattern when presented with a similar one.

The authors' moiré synaptic transistor could emulate this mechanism when programmed with a learning rule known as the Bienenstock–Cooper–Munro (BCM) model[7], which sets a dynamically updated threshold for strengthening or weakening a synapse that depends on the neuron's history. The BCM rule is an abstract algorithmic description of synaptic plasticity in the brain that has been connected to cognitive behaviours. By demonstrating that their device can implement this rule, Yan *et al.* have offered a pathway to recreating bio-realistic plasticity in human-made hardware.

Their work provides an opportunity for the BCM learning rule to act as a Rosetta Stone between theoretical neuroscience (much of which is based on BCM and similar models) and state-of-the-art neuromorphic computing.

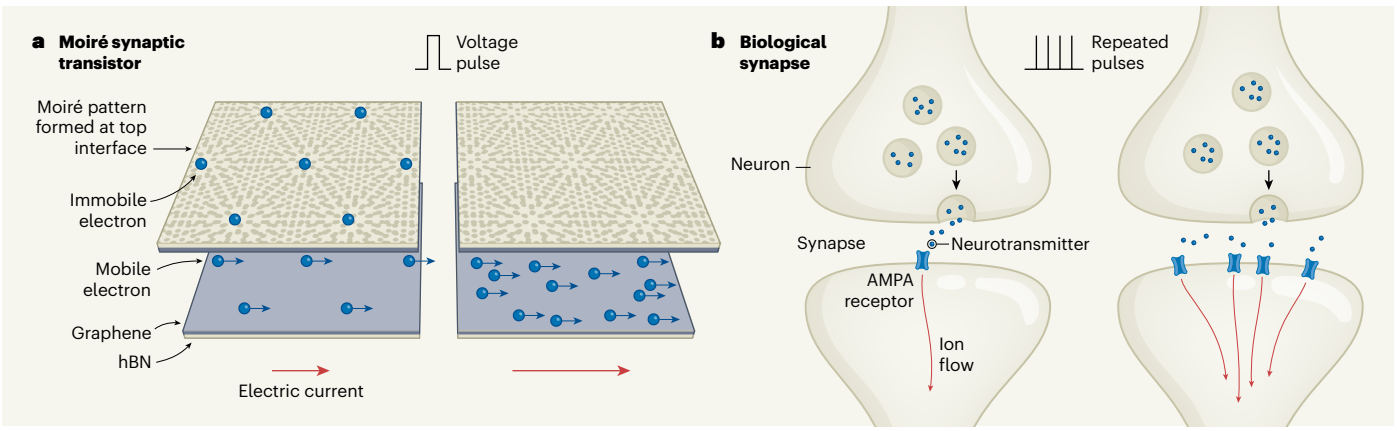

Figure 1 | A transistor that imitates a biological synapse. Yan *et al.*[1] built a device comprising two layers of graphene (each a single sheet of carbon atoms) and the dielectric material hexagonal boron nitride (hBN). **a**, The device is called a moiré synaptic transistor, because it shares similarities with synaptic connections between neurons, and because a 'moiré' pattern forms between the overlapping hexagonal crystal structures of the top layer of graphene and hBN. This pattern localizes electrons in the top graphene layer, but those in the bottom layer remain mobile. Applying a voltage pulse to the top gate (a component that regulates the number of electrons in the graphene system; not shown) results in a ratchet effect, through which an electric current is increased with successive pulses. **b**, This effect is reminiscent of the way in which repeated electrical stimulation can strengthen synapses by enriching protein complexes called AMPA receptors, leading to improved neurotransmitter efficacy and increased ion flow.

From the archive

Musings about correct scientific spelling, and an ancient Egyptian weighing balance.

100 years ago

May I follow Prof. Grenville Cole ... in supporting Sir Clifford Allbutt? The prefix "dino-," as thus spelled, is ambiguous. We who know that "dinosaur" means "terrible lizard" may smile at the undergraduate and his "dinnosaur." But how would you pronounce "Dinocystis"? Wrongly, no doubt, as I did myself until I learned that the first begetter of the name derived it from δίνειν, to swirl, because the rays are spirally coiled. The same for Dinocharis and Dinophysa ... [W]hat about the giant corkscrew shell from the Hastings Sand — the Dinocochlea of B. B. Woodward? That perhaps means "spiral coil"; or does it mean "monster coil"? Should it, in short, be Deinocochlea or Dinocochlea?

From *Nature* 22 December 1923

150 years ago

I have to thank Mr. Rodwell for calling my attention, in NATURE ... to the curious representation of an equal-armed Egyptian balance in a papyrus, now in the British Museum. This papyrus, which is perhaps the most beautiful in the whole collection, all the colours and lines being as bright and distinct as when originally painted, has been shown to me by Dr. Birch ... The heart of the deceased is being weighed in an equal-armed balance, and found lighter than a feather. In the papyrus, the weighing is being made in the Hall of perfect Justice, in presence of Osyris ... [W]hat Mr. Rodwell mentions as a sliding weight on one side of the beam, appears rather to be a loop or ribbon for limiting the oscillation of the beam. In the original papyrus the middle and both ends of the beam, as well as the lower part of the column, are coloured to represent polished brass, whilst the other parts of the balance are dark, as if of bronze. It should be observed that the balance beam has boxends for suspending the pans. Judging from the height of the human figures, the length of the balance beam represented is about six feet, and the height of the column ... is nearly the same.

From *Nature* 18 December 1873

For example, the authors' ingenious dual-gate control could be used to realize synaptic plasticity in the vestibulo-ocular reflex, the mechanism that stabilizes images on the retina as the head moves[8]. It will be interesting to see what other models of plasticity can be expressed, such as spike-timing dependent plasticity, in which the strengthening of a synapse is dependent on the timing of stimulation[9].

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Genetics

Indigenous diversity in Australia's DNA tapestry

Katrina G. Claw & Amber Nashoba

Diverse genomic sequences might boost equity in areas such as health care. Genomic data from Indigenous Australians, shared through a community-consultation framework, aids efforts to boost genetic representation. **See p.593**

Languages and genes can tell us stories of the past. The genetic differences between Indigenous Australian communities are not well understood but are hypothesized to reflect their linguistic diversity. On page 593, Silcocks *et al.*[1] present findings supporting this hypothesis, showing exceptionally high genetic variation and strong population structure (patterns of genetic variation resulting from past non-mixing) in genomic comparisons of linguistically distinct communities. The authors also highlight the importance of respecting cultural perspectives and engaging Indigenous Australian peoples in genomic research and its applications.

Australia, covering 7.6 million square kilometres, is geographically larger than the European Union (4.1 million square kilometres) and smaller than the United States (9.8 million square kilometres). More than 250 Indigenous languages are spoken in Australia, and these are an essential part of Indigenous medicine, identity and ancestral connections. Genetic analysis is another way to establish connections, because geographical patterns of genetic variation correlate with linguistic variation.

Worldwide, efforts to actively involve Indigenous ancestors (and their descendent communities) and peoples in genomic research are infrequent, with some research groups being more successful than others. In the past decade there have been several frameworks and guidelines published by Indigenous communities and stakeholders, describing current approaches and recommended improvements[2–4].

Silcocks *et al.* analysed data from the largest group (cohort) of Indigenous peoples to have had its genomes sequenced and published so far, with community consultation and input. The authors investigated how communities are related, working with Indigenous Australians to analyse full genomes of previously unanalysed speakers of certain Indigenous language groups.

Indigenous Australian peoples have lived for time immemorial on remote tropical islands, on northern coasts rich in biodiversity and beauty, and on lands nestled among the red sand dunes of the Simpson Desert in the centre of the country. Silcocks and colleagues present work sequencing 159 individual genomes from Indigenous Australian communities at four such sites (Fig. 1), and compare these data with some previously sequenced[5,6] genomes of 60 individuals from Papua New Guinea and its associated islands. The four sites were the Tiwi islands, Galiwin'ku and Yarrabah, all in the north of the country; and Titjikala in central Australia. Writing in *Nature*, Reis *et al.*[7] analysed DNA from the same cohort studied by Silcocks and colleagues to look at structural variation, examining the linear order of nucleotides in a genome and alterations to this order such as inversions, duplications and deletions.