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Condensed-matter physics

A twist in the bid to probe electrons in solids

Rebeca Ribeiro-Palau

Two microscopy techniques have been merged into a tool for twisting ultrathin sheets of atoms relative to each other. The approach offers a new angle for studying the electronic properties of exotic layered materials. **See p.682**

In 2018, scientists took two sheets of single-atom-thick carbon, called graphene, twisted them relative to each other by a 'magic' angle and observed a remarkable thing: the system conducted electricity without any resistance[1]. Efforts to characterize the properties of this intriguing twisted bilayer graphene began immediately, but the studies proved challenging[2]. Although it's tempting to imagine that the fabrication process is as easy as twisting two sheets of paper relative to each other, it's actually highly complex, because the fully aligned configuration is more stable than a twisted one. On page 682, Inbar *et al.*[3] report an exciting experimental technique for controlling the angular alignment of such layers *in situ* – perhaps the closest we'll come to the ideal scenario, equivalent to twisting two sheets of paper.

The authors began by studying how charge carriers move from one layer to the other, and the twist angles at which this motion (conduction) is allowed. A simple way to explain this is by analogy with two trains that cross paths along their route. If the trains move in the same direction and at the same speed, it's easy to jump from one train to the other. However, if they move at different speeds or in opposite directions, jumping from one to the other is almost impossible. This is because momentum is conserved – the person jumping needs to have the same momentum before and after the jump.

The same thing happens to charge carriers: they can move easily between layers only when their momentum before the jump matches that after the jump[4,5]. This simple but clever concept of momentum matching allowed Inbar *et al.* to develop a microscopy technique that they named the quantum twisting microscope. The approach takes advantage of the structural properties of 2D materials with atomically flat surfaces to explore the most fundamental quantum-mechanical property of a material, its energy dispersion – the way in which the energy of the electrons depends on their momentum.

Practically, Inbar and colleagues' technique is a merger of two existing microscopy tools: the atomic force microscope (AFM) and the scanning tunnelling microscope (STM), both of which involve scanning a sample using an extremely sharp tip. An AFM generates an image of the sample by measuring the forces between the tip and the sample, whereas an STM measures the current between the tip and the sample when a voltage is applied across them. The authors used these two capabilities to build a device that can control the angular alignment between thin sheets, and also measure the energy dispersion of the layered structure as it is manipulated *in situ*.

Inbar *et al.* first fabricated a pyramid-shaped AFM tip made from platinum, and deposited graphite and boron nitride on it. They then covered this tip with a layer of graphene so that it resembled a tent with a flat top. The authors installed the tip in an AFM and then brought the graphene into contact with another graphene layer; this had been placed on top of an angular rotator, which was used to control the angular alignment between layers (Fig. 1a). The contact area between the two layers was large (particularly compared with that in an STM), and this enabled the authors to investigate how the momentum matching between layers altered the charge-transport properties

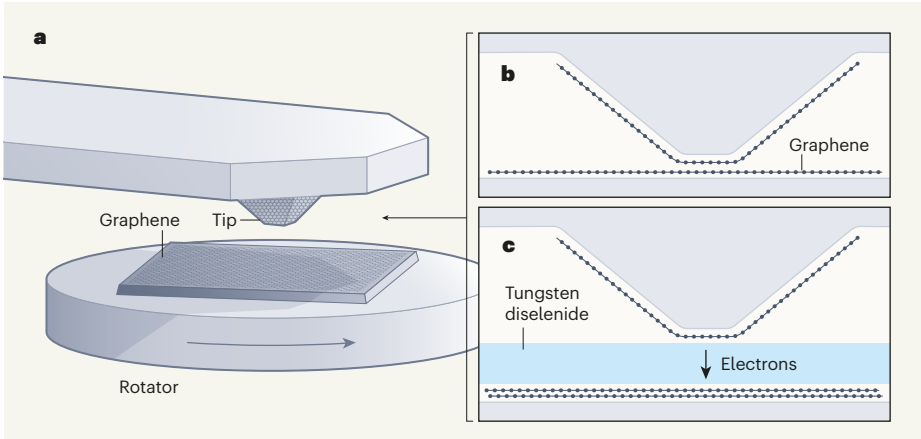

Figure 1 | The quantum twisting microscope. a, Inbar *et al.*[3] developed a tool called a quantum twisting microscope, which can be used to control the angular alignment between one or more sheets comprising single layers of atoms – such as graphene, which is made of carbon. The microscope consists of a pyramid-shaped metal tip that is covered in one sheet (of graphene, for example), and brought into contact with a second sample on a rotator. **b**, In this way, the microscope can be used to control the angular alignment of such layers *in situ*. **c**, The device can also measure and change the way in which the energy of electrons in the multilayered structure depends on their momentum. In this mode, the electrons move through an added layer of tungsten diselenide.

of the whole structure as they twisted the layers relative to each other (Fig. 1b).

They then went a step further by investigating the energy dispersion of the structure. To do this, Inbar *et al.* added a layer of tungsten diselenide, which acted as a barrier between the two layers of graphene, enabling the authors to measure the current that passed through the barrier (Fig. 1c). In this mode, the device functions in much the same way as does an STM.

The authors performed these experiments on graphene as a proof of concept. But they also showed that the approach could be used to probe systems with more complex energy dispersion; they did this using a tip covered with a single layer of graphene to probe a sample made from twisted bilayer graphene. Such experiments will enable researchers to better understand the electronic behaviours of systems such as twisted bilayer graphene, without the size restrictions associated with other experimental techniques. And by varying the pressure applied with the AFM tip, the authors showed that they could even alter the energy dispersion of twisted bilayer graphene. This approach improves on previous techniques involving challenging measurements of electron transport[6].

Inbar and colleagues' technique is truly remarkable, and will enable several key lines of research in condensed-matter physics. For example, physicists have long sought a technique for modifying the energy dispersion of samples *in situ* – a goal that Inbar and colleagues have made possible by applying pressure to change the angular alignment between layers. Their contribution is the latest in a list of technological developments that have improved and optimized 2D layered structures, such as twisted bilayer graphene.

The next logical step for this technique will be to develop the same experiments at low temperatures, at which the quantum phenomena associated with the modified energy dispersion are enhanced. It would also be interesting to combine the two types of experiment demonstrated by Inbar and colleagues – that is, to measure changes in the energy dispersion of a structure *in situ* as its layers are twisted relative to each other. But that might be a twist for a different story.

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Neurodegeneration

Alzheimer's risk gene works the gut–brain axis

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Signals from gut microorganisms to the brain might be involved in neurodegeneration. It emerges that the gene *APOE* – variants of which each confer a different risk of Alzheimer's disease – has a role in modulating this gut–brain communication.

The best biological marker of neurodegeneration is the accumulation of misfolded and aggregated proteins in the brain. These aggregates are often surrounded by brain-resident immune cells called astrocytes and microglia, tasked with removing debris and keeping neurons healthy[1]. Writing in *Science*, Seo *et al.*[2] identify a gene that determines how gut microorganisms affect such immune responses and protein aggregation in the brain. This gene, *APOE*, exists in three common forms (*APOE2*, *APOE3* and *APOE4*), of which *APOE4* confers the highest risk factor for late-onset Alzheimer's disease[3]. Seo and colleagues' work sheds light on how interactions between genes and the environment feed into neuro-immune crosstalk during neurodegeneration.

It is not uncommon for people who have neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease or amyotrophic lateral sclerosis to exhibit alterations to their immune systems and changes in the make-up of the bacterial communities that inhabit their guts[4,5]. In turn, this gut microbiota can regulate gene expression in microglia in a sex-specific manner[6], and a person's *APOE* status (that is, which of the *APOE* variants they carry) influences this process[7,8]. However, it is not clear whether disruption of the gut microbiota is a cause or a result of neurodegeneration. It is also not known whether timely correction of this gut dysbiosis could slow neurodegeneration.

Seo *et al.* set out to examine a strain of mice engineered such that a human form of tau, a protein associated with cognitive decline, accumulated in the animals' brains. The group genetically engineered these mice to express different forms of human *APOE*, and raised the animals in either a conventional environment or a germ-free environment (meaning that they lacked gut microbes). The authors found that the signs of neurodegeneration and neuroinflammation typically observed in conventionally reared animals carrying the high-risk variant *APOE4* were drastically reduced in animals raised under germ-free conditions (and so lacking a gut microbiota).

Similarly, Seo and colleagues found that diminishing the gut microbiota of the *APOE*-carrying animals using antibiotics mitigated neurodegeneration. Interestingly, the protective effect of both antibiotic treatment and germ-free rearing was more pronounced in male mice harbouring *APOE3* (a variant that does not confer as much risk as *APOE4*)[3] than in males carrying *APOE4* or in females.

Some evidence[9,10] suggests that short-chain fatty acids (SCFAs) produced by the gut microbiota could be involved in modulating astrocyte and microglia functions (such as the production of signalling molecules called cytokines). It is not known whether SCFAs act directly on brain cells, but Seo *et al.* demonstrated that, as well as reducing SCFA levels, the antibiotic treatment reduced the numbers of various types of immune cell in the meninges (tissues that border the brain) in *APOE3*-carrying mice; it also altered gene expression in lung immune cells called alveolar macrophages (Fig. 1). These cell types also release cytokines that might signal to the brain, and might present antigen molecules to circulating immune cells called T cells that, in turn, could move to the brain to trigger neuroinflammation. This finding is interesting because the role of crosstalk between immune cells in the body and brain is not yet fully understood in the context of neurodegenerative disease[11].

Finally, the researchers added SCFAs to the drinking water of germ-free mice carrying *APOE4*. This SCFA administration altered gene expression in alveolar macrophages, increased the proliferation of astrocytes and microglia (a process known as gliosis) and exacerbated neurodegeneration. The results raise the possibility that SCFAs might be key mediators of the microbiota's effect on tau-mediated neurodegeneration. The clear next steps are to delineate the direct mechanisms by which these fatty acids act, the cell type that they target, and how *APOE* status matters in