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the authors found that the tag binds to large intracellular structure(s), making it invisible to NMR and thus simplifying the in-cell NMR spectrum of the target protein.

This method opens the door to determining protein structures inside human cells in the near future, but has already been used by Inomata *et al.* to study in-cell protein dynamics. For example, macromolecular crowding inside the cell should stabilize protein structures. Inomata *et al.* show that, for at least one protein, ubiquitin, introduced into a human cell at physiological concentrations, the opposite is true. Ubiquitin becomes more dynamic in its reactivity and less structured, presumably due to nonspecific, low-affinity interactions with its binding partners. This unexpected result highlights the importance of studying proteins inside living cells.

In-cell NMR is limited by the concentration and structural stability of the protein that can be attained inside cells. In addition, some proteins could be difficult to deliver into the cytosol by fusing them with cell-penetrating peptides. Very large proteins, or proteins that bind to large cellular structures, become invisible and cannot be effectively studied by in-cell NMR. The lifetime of the cells is also a limiting factor, because cell breakdown results in protein leaking away into solution, the condition of *in vitro* NMR. Despite these pitfalls, we are left with an enormous number of proteins that can be studied.

Exploring protein structures and dynamics at the atomic level inside living cells will provide results that cannot be obtained using standard *in vitro* techniques. The comparative simplicity of the in-cell method allows for a myriad of applications. The regulation of metabolic or signal-transduction pathways, mediated by biomolecular interactions, can now be studied in detail. Drug screening using in-cell NMR can function as an *in vivo* assay at atomic resolution, providing information about drug delivery inside the cell, where the drug binds, and whether there is a notable difference between how it binds *in vivo* and *in vitro*. More exotic applications include the study of intrinsically unstructured and amyloid-forming proteins in neurons — such proteins having been implicated in neurodegeneration — or of labelled protein probes in diseased tissue. The ability to observe the structures of proteins in their native environment releases the constraints that have previously limited study of protein structure and dynamics to the test tube. Now that structural biology has moved into the cell, it is likely to stay there. ■

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CONDENSED-MATTER PHYSICS

Carbon conductor corrupted

Michael S. Fuhrer and Shaffique Adam

Atomically thin sheets of graphite are metal-like conductors — until they react with hydrogen, when they become insulators. This curious effect could be an excellent model for studying metal–insulator transitions.

In most solids, electrons behave much like particles of matter: they have a mass, and they speed up and slow down in response to forces. But in graphene — the single-atom-thick sheet of carbon that constitutes the basic building block of graphite — electrons move as if they have no mass[1,2], and so behave more like photons. In other words, although electrons in graphene can change their momentum and energy, they cannot speed up or slow down. One would therefore intuitively think that electron flow (electrical current) in graphene could never be completely blocked. But reporting in *Science*, Elias *et al.*[3] show that, when graphene reacts with a small amount of hydrogen, its electrons become stuck and the carbon sheet becomes an insulator.

The band structure of a material describes which energy states can be occupied by the material's constituent electrons. Just like other fermions, electrons in a solid fill up the lowest-energy bands first, before filling up bands at higher energies, like water filling a bath. If electrons at the top surface — the Fermi level — of the resulting electron sea can slosh about into the unoccupied part of the band structure, then the solid is said to be a metal, in which electrical currents are created by electrons moving from one momentum state to another (Fig. 1a). But if the electrons are not free to move because of a gap in the band structure, then the solid is a 'band insulator' (Fig. 1b).

There is, however, another way to make an insulator. Electrons are quantum-mechanical objects that behave as waves. Constructive interference of electron waves near any imperfections — disorder — in a solid creates standing waves (Fig. 1c) that are localized in real space, effectively 'freezing' the electron sea[4]. A long-standing conjecture in physics states that electrons in any two-dimensional system will become localized by any disorder, no matter how small. Because all two-dimensional electronic systems contain some disorder, all such systems should therefore be insulators[5]. In practice, however, very low temperatures and/or large samples are needed to reveal this insulating behaviour, and even then the effect is not always seen.

So how does graphene fit into all this? The band structure of graphene can be thought of as a cone balancing on its tip, atop the point of another cone (Fig. 1d). Because there is no bandgap, graphene is a metallic conductor. But graphene differs from other metals when its Fermi level lies at the Dirac point — the point where the cones touch. There, the top surface of the electron sea becomes vanishingly small. One consequence is that, in contrast to disorder-free metals (which would have infinite conductivity), perfect sheets of graphene are expected to have a conductivity of $4e^2/\pi h$, where e is the electronic charge, and h is Planck's constant. Furthermore, graphene is thought to be the only exception to the localization conjecture: if it contains only 'smooth' disorder in which there are no sharp changes between neighbouring carbon atoms, then graphene remains metallic, and even quantum interference cannot localize its electrons[6].

In reality, graphene is found to have a sample-dependent, finite minimum conductivity that is always greater than $4e^2/\pi h$ (ref. 1), thus creating a mystery — how could the disorder present in real graphene increase the conductivity above the theoretical value for perfect graphene? Disorder normally increases the scattering of electrons, which decreases conductivity.

The answer lies in the nature of the disorder. Most graphene samples are dirtied by charged impurities that lie near the graphene sheet, either on the surface or in the nearby substrate[7]. These charges have two effects: they create a smooth disorder that scatters electrons (which reduces conductivity), but they also either attract or repel electrons, creating local electron-rich or electron-poor 'puddles' whose Fermi levels lie above or below the Dirac point. The electrons in these puddles increase the conductivity of the sample, counteracting the decrease due to scattering[8].

By adding hydrogen to graphene, Elias *et al.*[3] were able to study a fundamentally different sort of disorder. By reacting all the carbon atoms in a graphene sheet with hydrogen, so that each carbon becomes bonded to a single hydrogen atom, the authors made a new kind of two-dimensional crystal. This material, known as graphane, is expected to be a conventional band insulator[9].

But at lower doses, hydrogen probably bonds randomly to only a few carbon atoms. Unlike charged impurities, which cause a smooth disorder, hydrogen creates sharply varying disorder, because a carbon atom bonded to hydrogen is very different from its neighbours. The authors[3] observed that their partially hydrogenated graphene had greatly reduced minimum conductivity, which varied with temperature and tended towards zero at low temperatures — the signature of an insulator. This is in contrast to graphene containing

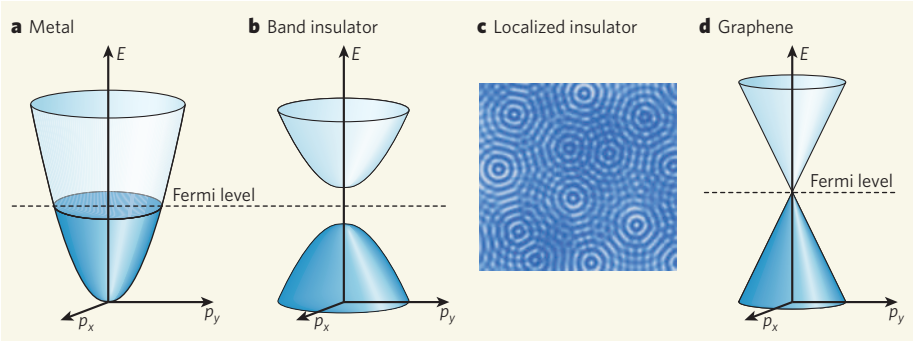

Figure 1 | Metal–insulator transitions. **a**, The electronic energy states of metals form a series of bands. Electrons fill the bands up to a maximum energy defined by the Fermi level. *E* is energy, *p* is momentum. **b**, The Fermi level of a band insulator lies in a gap in its band structure. Electrons completely fill the lower valence band, but do not cross into the upper conduction band, and so are not free to form a current. **c**, Imperfections in solids scatter electrons, creating standing waves that also prevent the motion of electrons, so resulting in a localized insulator. **d**, The electronic energy-states of graphene form two cone-shaped bands that meet at their tips. In charge-neutral graphene, the Fermi level lies at the tip of the cones. There is no bandgap, so the material is classed as a metal. Elias *et al.*[3] show that when graphene reacts completely with hydrogen, it forms a new material (graphane) that is expected[9] to be a band insulator. Reaction of graphene with smaller amounts of hydrogen (also demonstrated by Elias *et al.*) might produce sharp imperfections that bring about a localized insulating state.

charge disorder, where the conductivity is temperature-independent at low temperatures[1].

Why are the effects of charged impurities different from those caused by bonding to hydrogen? The unique properties of graphene prevent the slowly varying potential of a charged impurity from completely backscattering (reversing the direction of) electrons. An exciting possibility is that sharp disorder caused by hydrogen can easily backscatter electrons. The resulting interference of forward- and backward-moving electrons would create localized states at zero temperature, just like those found in other two-dimensional systems[10]. Another possibility is that hydrogen locally modifies the band structure of graphene, so creating a band insulator.

More work will be needed to understand both the electronic structure of hydrogenated graphene and the effects of sharp and smooth disorder on the scattering of its electrons. Nevertheless, these results[3] suggest that graphene could be almost the ideal material in which to study transitions of metals to insulators. Unlike other two-dimensional systems, in which electrons are buried at the interface between two materials, graphene's surface is exposed. This allows not only direct imaging of defects by scanning tunnelling microscopy, but also the use of techniques that probe electronic structure, thus creating new windows through which metal–insulator transformations can be viewed. ■

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DRUG DISCOVERY

Not as fab as we thought

Soumaya Zlitni and Eric D. Brown

Ever since penicillin was isolated from mould, it has been assumed that naturally occurring antibiotics are good starting points for drug-discovery programmes. The latest study shows that this isn't always true.

Drug-resistant bacterial infections continue to occupy the headlines, amid increasingly desperate calls for new antibiotics to treat infectious diseases. Some of the most alarming reports concern 'Gram-positive' pathogens[1], which are a pervasive nuisance in both the clinic and the world at large. The recent discovery[2] of the potent antibiotic platensimycin was therefore greeted with great enthusiasm. Platensimycin was isolated from soil-dwelling *Streptomyces platensis* microbes, and represents a new class of antibiotic that acts against Gram-positive pathogens. But on page 83 of this issue, Brinster *et al.*[3] provide a sobering lesson in what drug discoverers call target validation. The authors show that, although compounds that have the same mechanism of action as platensimycin are effective antibacterials in soil, they are inactive in models that simulate environments relevant to infection.

The problem with existing antibiotics is that they attack a narrow spectrum of bacterial physiology: most interfere with the synthesis of bacterial DNA, proteins or cell walls. There is therefore great interest in exploring new biological targets for antibacterial therapies. One potential target is fatty-acid biosynthesis, and the past few years have witnessed intense efforts to identify inhibitors of this process.

Fatty acids are organic molecules that contain long, unbranched hydrocarbon chains of up to 18 carbon atoms. Their biosynthetic machinery is encoded by several genes involving the *fab* loci of the bacterial genome. Fab proteins come together to construct fatty acids, two carbon atoms at a time, in a cyclic process. The promise of this biosynthetic pathway as an antibacterial target stems from the fact that it is essential for the formation of cellular membranes in a wide range of bacterial pathogens. The process is distinct from fatty-acid biosynthesis in humans, suggesting that antibiotics that block this mechanism could be made that are selectively toxic for bacteria.

Several compounds have already been identified that inhibit specific steps in the bacterial biosynthesis of fatty acids. These include synthetic compounds (such as the antituberculosis compound isoniazid and the general-purpose antibiotic triclosan) and naturally occurring compounds (such as cerulenin and thiolactomycin, both broad-spectrum antibiotics)[4]. The synthetic compounds, however, have had only niche applications — isoniazid in combination therapies and triclosan in soaps and plastics — whereas the natural products have never proved useful in the clinic. Nevertheless, the discovery of platensimycin as a new addition to the roster of fatty-acid biosynthesis inhibitors generated renewed excitement about this antibiotic class.

Yet studies dating as far back as the late 1970s have shown that Gram-positive bacteria can acquire fatty acids from their surroundings and incorporate them into their cell membranes[5]. Given that human serum is a rich source of such acids, these findings seriously undermine the idea that inhibitors of bacterial