

coupling elements and have even identified some pair-wise interactions, the real novelty of Lee and Sine's work is that it teases apart the functional interactions between these different regions on an atomic scale. Their data provide a detailed molecular scaffold for the idea that the binding of neurotransmitter triggers a wave of conformational changes that propagates from the ligand-binding site to the pore through the membrane<sup>8</sup>.

One particularly attractive feature of Lee and Sine's model is the electrostatic interaction that exists between a positively charged arginine residue in the preM1 region and a negatively charged glutamate residue in loop 2 (Fig. 1c). Charged residues occur in these positions in every member of this receptor superfamily, suggesting that it is a common mechanism for linking binding-site changes to loop 2. Loop 2 sits above the extracellular end of the M2 helix that forms the channel, next to the M2–M3 loop, and one can easily envisage how movements in loop 2 could be conveyed to the channel through interactions between residues in these two regions<sup>9–11</sup>. Lee and Sine found several interacting residues, in particular a proline in the M2–M3 region (Fig. 1c). And this is where the work by Lummis *et al.*<sup>3</sup> comes in — their study concentrated on a proline in exactly the same position in the serotonin 5-HT<sub>3</sub> receptor.

Proline residues are unique in that their side chains are covalently bonded to the nitrogen atom of the protein's peptide backbone. The nitrogen atom of a peptide bond is usually involved in secondary interactions with other parts of the protein, helping to hold helices together, for example; but at proline, these secondary interactions are disrupted. In addition, proline is the only natural amino acid for which two different conformations of the peptide bond (*cis* and *trans*) are possible. These properties allow prolines to act as molecular hinges or switches<sup>12</sup>.

In an elegant study on 5-HT<sub>3</sub> receptors, Lummis *et al.*<sup>3</sup> replaced the proline in the M2–M3 loop with a series of synthetic amino acids that had different propensities for adopting *cis* versus *trans* conformations. Amino acids that favoured the *cis* conformation resulted in receptors with high apparent affinities for neurotransmitter, producing ligand-induced 'locked' open channels. Amino acids that mostly took on *trans* conformations resulted in unresponsive closed channels. So it would seem that the conformation of the M2–M3 proline is coupled with the conducting state of the channel, pointing to the proline as a gating switch.

Taken with Lee and Sine's work, this conjures up a mechanism in which neurotransmitter binding to the receptor sets in motion a cascade of structural movements that end up flipping the proline to the *cis* conformation. This results in a repositioning of the M2 channel-lining region, such that the channel pore opens.

Although the two studies tell a compelling story of how ligand binding is translated into channel opening, it is probably not complete. The proline residue in the M2–M3 loop of the acetylcholine and serotonin receptors does not occur in the receptors for GABA or glycine, so other mechanisms must be invoked to explain how they open. Changes between *cis* and *trans* proline conformations are generally slow, so we need to determine whether this switch is fast enough to open channels on a sub-millisecond timescale. And because other regions and residues are involved in coupling binding to gating, the activation pathway charted by Lee and Sine will probably have others feeding into it. Finally, ligand-gated ion channels not only open and close in response to binding neurotransmitter, but they also become desensitized (close) in the continued presence of neurotransmitter. How this occurs is still a mystery. ■

## MATERIALS SCIENCE

# Erasing electron mass

Charles L. Kane

**Two-dimensional graphite could be useful in carbon-based electronic devices. How electrons move in these structures seems best described by relativistic quantum physics, modelling them as if they have no mass at all.**

Graphite, the form of carbon found in pencil lead, leaves its mark thanks to weakly coupled layers of atoms that slide easily over one another. A single such layer — a two-dimensional sheet of carbon a single atom thick — is known as graphene. Although graphene has been studied for decades, graphene was only isolated in 2004 after a long struggle. The successful method was astonishingly simple: starting with a graphite crystal, layers of carbon atoms were peeled off one by one with adhesive tape, until a single-layer flake was left<sup>1</sup>. In this issue, Novoselov *et al.* (page 197)<sup>2</sup> and Zhang *et al.* (page 201)<sup>3</sup> investigate the properties of graphene further, showing it to be a remarkable conductor in which electrons mimic the behaviour of massless, relativistic particles.

In graphene, the carbon atoms are arranged in a honeycomb pattern (Fig. 1a), with each atom bound to three neighbours through strong, covalent bonds. This gives graphene exceptional structural rigidity within its layers. Because a carbon atom has four electrons available for bonding, each atom also contributes one unbound electron that is free to wander through the crystal, giving graphene its second distinctive characteristic — excellent conductivity.

The mobile electrons in graphene seem to behave differently, however, from those in two-dimensional semiconductor structures. In semiconductors, an electron can be

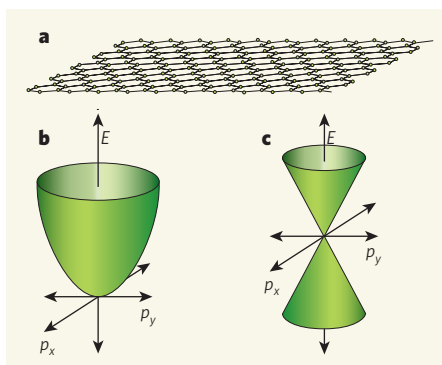
Cynthia Czajkowski is in the Department of Physiology, University of Wisconsin-Madison, 601 Science Drive, Madison, Wisconsin 53711, USA. e-mail: czajkowski@physiology.wisc.edu

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modelled as a particle that obeys Newton's laws of motion, provided it is ascribed an effective mass,  $m^*$ , which takes into account the interaction between the electron and the semiconductor's crystal lattice. Electrons in semiconductors are thus characterized by a quadratic relationship between energy and momentum (Fig. 1b), and their quantum-mechanical behaviour can be described by the non-relativistic quantum theory formulated in the Schrödinger equation.

In contrast, the observations of Novoselov *et al.*<sup>2</sup> and Zhang *et al.*<sup>3</sup> show that, in the honeycomb structure of graphene, the relation between energy and momentum of the conduction electrons is linear (Fig. 1c). This is reminiscent of Einstein's theory of relativity for massless particles — which travel at the speed of light — and suggests that electrons in graphene obey a two-dimensional version of the relativistic quantum theory introduced by Paul Dirac in 1928. Electrons in graphene are, of course, not actually massless, and their typical speed ( $8 \times 10^5$  m s<sup>-1</sup>) is almost 400 times lower than the speed of light in a vacuum (about  $3 \times 10^8$  m s<sup>-1</sup>) — although still much higher than the speed typical of electrons in semiconductors.

The conclusions of the authors<sup>2,3</sup> are based, to a large extent, on their observation of the quantum Hall effect in graphene. This phenomenon is the quantum-mechanical



**Figure 1 | Slim, strong and a live wire.** **a**, The honeycomb lattice pattern of graphene explains its strength and good conductivity. Each carbon atom (green dot) uses three of its outer valence electrons to form strong covalent bonds, leaving one left over that is available for conduction. **b**, The quadratic, newtonian energy-momentum relation,  $E = p^2/2m^*$  ( $E$ , energy;  $p$ , momentum;  $m^*$ , reduced mass) is obeyed by electrons in a semiconductor. **c**, The energy-momentum relation of electrons in graphene is quite different,  $E = v|p|$  ( $v$  is the electron velocity), allowing them to be modelled as massless, relativistic particles according to the Dirac formulation of quantum mechanics.

analogue of an effect observed by Edwin H. Hall in 1879 in a macroscopic conductor. In a magnetic field, charged particles such as electrons experience a force perpendicular to their motion, causing them to move in closed circles. A magnetic field applied at right angles to the surface of a conductor will therefore deflect the electrons from their path between the terminals, establishing a voltage perpendicular to the direction of current flow. In a conventional solid, the Hall resistance (given by the ratio between the perpendicular voltage and the forwards electron current) increases smoothly as the applied magnetic field increases.

In a two-dimensional solid at low temperatures, however, quantum effects — specifically, the wave-like properties of the electrons — come into play. Only an integer number of electron wavelengths may fit into the circular orbits induced by the magnetic field, restricting the permitted electron energies to a set of discrete, quantized values. This means that in turn the Hall resistance no longer increases continuously with increasing magnetic field strength, but in a characteristic series of steps quantized in units of  $h/e^2$  (where  $h$  is Planck's constant and  $e$  the electron's charge). Since its discovery in 1980, this quantum Hall effect has had a profound impact on semiconductor research, with two Nobel Prizes in Physics — those of 1985 and 1998 — being awarded for work on it.

Both Novoselov *et al.*<sup>2</sup> and Zhang *et al.*<sup>3</sup> observed quantized steps in the Hall resistance of graphene — a result that highlights the exemplary quality of their samples. The exact numerical values at which the resistance steps occurred were, however, found to be shifted by one-half of a unit from those expected for non-relativistic electrons. The relativistic

theory provides an explanation: just as Dirac's original theory explained why electrons have an intrinsic angular momentum, known as spin, the effective Dirac theory for graphene endows electrons with an additional 'pseudospin'. When an electron completes a circle in an applied magnetic field, its pseudospin rotates by  $360^\circ$ . As is the case for real spin, such a rotation introduces a  $180^\circ$  phase shift in the electron wave, so an additional half wavelength must fit in the circumference of the circle, changing the pattern of allowed energies. The pattern of the observed steps<sup>2,3</sup> in the Hall resistance fits with this picture perfectly, providing convincing evidence for graphene's Dirac electronic structure.

The electrical conductivity of graphene at zero magnetic field, with a minimum value at low temperature that is close to  $4e^2/h$  for several different samples<sup>2</sup>, raises interesting

questions. Such a 'universal' minimum conductivity is in itself reasonable; how to explain the precise value, however, is an open question. Away from the minimum, the conductivity varies linearly with electron density — expected for newtonian electrons, but surprising for relativistic electrons. Finding answers to these remaining riddles will be essential for realizing the potential of graphene-based electronics. So it's time for theorists to sharpen their pencils. ■

Charles L. Kane is in the Department of Physics and Astronomy, University of Pennsylvania, 209 S. 33rd Street, Philadelphia, Pennsylvania 10104, USA.

e-mail: kane@physics.upenn.edu

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## MICROBIOLOGY

# RAMP resistance

Angus Buckling and Michael Brockhurst

**There is an urgent need for new antimicrobial agents because antibiotic resistance has become so prevalent. But a promising class of such agents, known as RAMPs, may suffer from the same problem.**

In a report published in *Proceedings of the Royal Society*, Perron *et al.*<sup>1</sup> demonstrate experimentally that bacteria can readily evolve resistance to a group of proteins called ribosomally encoded antimicrobial peptides (RAMPs). RAMPs are produced by animals, plants, fungi and bacteria as part of their natural defence against microbial attack<sup>2–4</sup>, and are being developed as antibiotics. But because bacterial resistance to chemotherapeutic RAMPs could confer resistance to the battery of innate human RAMPs<sup>4</sup>, the worrying prospect is that widespread use of these agents may compromise our natural defence against bacteria.

With the emergence of bacteria that are resistant to 'last resort' antibiotics such as vancomycin<sup>5</sup>, there is a desperate need to identify new antimicrobial agents. RAMPs may be just such agents. They are a diverse group of proteins, and their mode of action varies considerably, but a common feature is their positive charge. This allows them to bind to the negatively charged membranes of bacteria. The effectiveness of a variety of RAMPs in clinical trials<sup>2,3</sup>, and the recent discovery of fungus-derived RAMPs that can be produced in large yields<sup>3</sup>, suggest RAMPs could be in widespread clinical use within the next few years.

The potential advantages of RAMPs are the apparent difficulty that bacteria face in evolving resistance to them, and the fact that resistance to conventional antibiotics does not seem to confer resistance to RAMPs<sup>2</sup>. Bacteria have

obviously encountered RAMPs in one form or another for millions of years, yet widespread resistance is rare. Furthermore, previous experimental tests suggest that the evolution of resistance does not readily occur<sup>6,7</sup>.

However, resistance evolution is all about the level of exposure. Although bacteria had been exposed to natural antibiotics such as penicillin and streptomycin (respectively produced by the *Penicillium* mould and *Streptomyces* bacteria) for millions of years, resistance was at low levels when widespread clinical use of these drugs began in the 1940s. But after a few years of exposure to high clinical doses, resistance was widespread in many species of pathogenic bacteria.

On the basis of such logic, Perron *et al.*<sup>1</sup> attempted to experimentally induce resistance to a RAMP in two different bacterial species, *Escherichia coli* and *Pseudomonas fluorescens*. The RAMP in question, pexiganan, is a synthetic analogue of a RAMP derived from toads (magainin) that has been modified for use as a chemotherapeutic agent. The authors exposed bacteria to slowly increasing concentrations of the drug for 600 generations (a few months in the lab), unlike previous work where drug concentrations were kept constant, and populations were allowed to evolve for no more than 200 generations<sup>6,7</sup>. The results were astounding: 22 out of 24 populations of bacteria had developed resistance to the drug.

The ability of bacteria to evolve resistance to