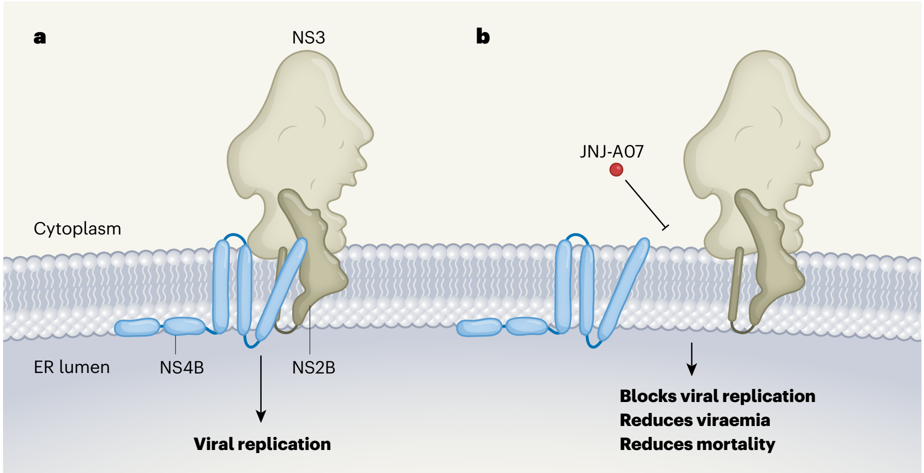

Figure 1 | A molecule called JNJ-A07 inhibits the replication of dengue virus. It has been challenging to find therapeutics for dengue disease. **a**, Replication of dengue virus, the agent that causes the disease, requires the formation of a complex that includes the viral proteins NS4B, NS3, NS5, NS2A, NS2B, NS4A and NS1 in the membrane encapsulating an organelle called the endoplasmic reticulum (ER) in host cells (NS4B, NS2B and NS3 are shown here). **b**, Kaptein *et al.*[2] identify a molecule called JNJ-A07 that can be delivered orally and reduces the levels of dengue virus in the blood of infected mice, when used preventively or therapeutically (after infection). The authors propose that JNJ-A07 blocks the binding of NS4B to NS3, preventing the formation of the viral replication complex and thus inhibiting viral replication, reducing both the amount of virus in the blood (viraemia) and mortality.

animals infected with DENV that have intact interferon signalling.

A property shown by the four DENV serotypes is that the presence of virus in the blood (known as viraemia) in an initial DENV infection usually results in a robust antibody response that provides protection against future infection and disease by the same serotype, as well as in the production of antibodies that cross-react with other DENV serotypes. If an individual's immune system produces a low-to-intermediate level of certain cross-reactive antibodies, there is an increased risk of more-severe disease after a subsequent infection with a different DENV serotype, through a phenomenon called antibody-dependent enhancement[5]. Therefore, when an infection is suppressed by an antiviral that lowers viraemia, does this alter antibody production in such a way that an individual is predisposed to antibody-dependent enhancement in a subsequent infection? This question must be considered when developing a dengue therapeutic.

Although JNJ-A07 displays excellent efficacy in the authors' mouse model, it is worth investigating whether combining this compound with other promising dengue therapeutics would yield synergistic antiviral activity against infection[6]. Candidates for possible therapeutics to combine include — but are not limited to — inhibitors of an enzyme called viral RNA-dependent RNA polymerase[7] (which catalyses the replication of the virus's RNA), or even other NS4B inhibitors, such as the compound NITD-688, which was shown to be highly effective in mouse models and targets NS4B through a potentially different mechanism from that of JNJ-A07 (ref. 8).

In summary, the authors have discovered an orally administered DENV-specific NS4B inhibitor that is effective against all four DENV serotypes, with a high barrier to resistance, a previously undescribed mechanism of action, and efficacy against one DENV serotype when administered preventively or therapeutically in mice. Although JNJ-A07 is not the first dengue NS4B inhibitor to be discovered[8–11], it is one of the most promising and well characterized. As such, the next challenge is to design clinical trials for JNJ-A07 in humans, paying particular attention to its use (preventive or therapeutic), the clinical outcomes (in treating non-severe or severe disease) and the target population (individuals who live in areas where dengue is endemic, or people visiting or travelling through such areas)[12].

Beyond this, ensuring that people with dengue seek treatment early in the viraemic phase of infection is a challenge that all dengue antiviral programmes will need to address. However, people could be more incentivized to seek treatment if they knew that a therapeutic finally existed. Although such challenges will be complicated to address, the fact that they can now even be considered represents a major advance in the field of dengue therapeutics.

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Applied physics

Non-magnetic objects moved by electromagnets

Eric Diller

A set of electromagnets has been used to move metal objects without touching them, even though the objects are not magnetic. This method could potentially be used like a 'tractor beam' to move hazardous objects in space. **See p.439**

Imagine trying to catch a fragment of a rocket nozzle in orbit above Earth's atmosphere. The fragment is travelling faster than a bullet, and tumbling rapidly end over end. Around 27,000 orbiting pieces of such debris are large enough to be tracked by the US Space Surveillance Network, and they constantly threaten active spacecraft and satellites. If the debris were magnetic, then magnets could be used to safely grab hold of the objects and dispose of them — but orbital debris tends to contain little or no magnetic material. On page 439, Pham *et al.*[1] report a method that allows magnets to grab non-magnetic objects from a distance,

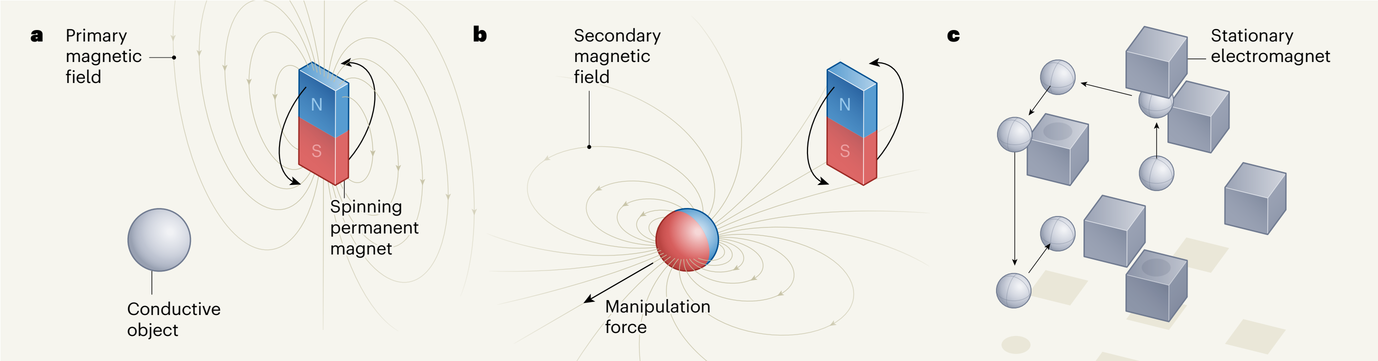

Figure 1 | Manipulation by magnetic induction. a, A changing magnetic field can be produced by an electromagnet or, as shown here, a rotating permanent magnet. When an electrically conductive object is placed in the changing magnetic field, internal electrical currents (not shown) are induced and form loops inside the object. **b**, These loops generate a secondary magnetic field that repels the primary permanent magnet, pushing the conductive object away from the permanent magnet in a perpendicular direction. **c**, Pham *et al.*[1] report simulations showing that an array of electromagnets can be used to generate magnetic fields that move and manipulate conductive objects in three dimensions while controlling their orientation, through magnetic induction. The approach was also demonstrated experimentally in 2D (not shown).

which could potentially be used by clean-up satellites for debris capture and disposal.

Magnetic fields can be used to push, pull and turn magnetic objects from a distance – this principle is used in electric motors to rotate the motor's shaft. Sophisticated motion control using magnetic fields is also possible, allowing magnetic objects to be manipulated in three dimensions with dexterity and speed[2]. But, because these methods are limited to objects containing magnetic materials, they cannot be used for many applications.

The non-contact manipulation method introduced by Pham *et al.* allows a non-magnetic object to be pushed, pulled and turned in three dimensions, as long as the object is made from an electrically conductive material such as metal (Fig. 1). The authors make use of a phenomenon known as magnetic induction, in which a fast-changing magnetic field induces an electrical current in a conductor, thereby turning the conductive object into a magnet. Magnetic induction has been used since the 1800s to wirelessly transmit energy between conductors across short distances. Uses range from electrical transformers, which are ubiquitous in modern electronics and electrical power-delivery networks, to wireless-charging smartphones and induction cookware.

Electrical currents induced by alternating magnetic fields form loops (known as eddy currents) within the conductor in which they are produced. These eddy current loops in turn produce their own, secondary magnetic field. In this way, a changing magnetic field can turn any conductor into a secondary electromagnet. The secondary electromagnet will then exert magnetic forces on the source of the original magnetic field. If the original magnetic field is produced by a moving or rotating magnet, the induced force opposes the original motion, and acts to slow the magnet's movement. This drag effect is used as a passive braking system for some trains. The force induced by electromagnets can also be harnessed to undertake work in industrial motors and magnetic propulsion systems for rollercoasters, and even to launch projectiles from advanced artillery known as railguns. In these applications, the force controls the motion of mechanism components along prescribed axes. Pham *et al.* have generalized this approach to manipulate free-moving conductive objects in three dimensions.

Inductive manipulation of non-magnetic free-moving objects has been previously reported, using stationary or rotating permanent magnets[3,4]. These inductive manipulation methods have been explored for potential applications such as the non-contact manipulation of space debris and even to drive the traversal of a repair or inspection robot along the exterior of the International Space Station. But these methods are able to produce forces only in limited directions and rely on the use of large and heavy permanent magnets.

> **"Safely grabbing and pushing orbital debris is a major challenge because the pieces can spin rapidly."**

Pham *et al.* have taken a different approach: they use an array of electromagnets to generate rotating magnetic fields along any axis. The authors show in numerical simulations that the generated fields can move non-magnetic objects along any axis in 3D, while controlling the objects' orientation. They also demonstrate the general manipulation capability of their approach experimentally in 2D, by using it to move a copper sphere in a plane. To simulate the low-friction environment of free movement in space, they floated the conductive sphere using a raft in a tub of water (see Fig. 3e–g of the paper[1]).

The authors' method has great potential for manipulating and clearing up orbital space debris. The rapidly increasing quantity of such debris threatens to make the highly useful low Earth orbit – the area of space up to an altitude of 2,000 kilometres, where most satellites and all crewed spacecraft orbit – unusable if a method to clean it up is not found[5].

Orbital debris largely consists of aluminium, a non-magnetic but highly conductive metal. Myriad solutions have been proposed to capture pieces of debris and drag them to a lower atmospheric orbit, where they would burn up. However, safely grabbing and pushing orbital debris is a major challenge because the pieces can spin rapidly. Pham and colleagues' non-contact magnetic manipulation method, acting like a science-fiction 'tractor beam', is a promising approach for safely slowing the tumbling of each piece and towing it to a lower orbit for disposal.

It should be noted, however, that Pham and co-workers' experimental demonstration is limited to motion in a single plane. The induction effect also dies off quickly as the gap between electromagnet and object increases – in the reported experiments, the gap between actuating electromagnets and the object is only about 5–10 centimetres. Moreover, the manipulation forces generated by the method are small, which makes the weight of the object a substantial hurdle to overcome in a terrestrial set-up. In space, where object weight is not a factor, these low forces could be perfectly adequate for slow manipulation. It will be difficult to demonstrate that full 3D manipulation is possible using this method without being in orbit.

There is also room to further optimize the algorithm used to control the electromagnet array – Pham *et al.* simplified the algorithm by considering only a subset of possible electromagnet inputs. By considering the continuum of all possible inputs, faster and stronger manipulation could be achieved, which would further help in the application of this concept.

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Neuroscience

Flies sense the world while sleeping

Wanhe Li & Alex C. Keene

High-throughput analyses of how sleeping fruit flies respond to a variety of odours show that the brains of these insects continue to process the value of the signals conveyed by sensory information during sleep. **See p.479**

Sleep is a complex behaviour nearly ubiquitous among animal species[1,2]. Many animals, including humans, are less responsive to sensory stimuli during sleep than when they are awake. However, human sleep is unlikely to involve a complete loss of consciousness, because people respond to salient stimuli – such as the sound of names[3] or a baby crying – during sleep, while filtering out more-trivial sensory cues. But whether other animals can evaluate the importance or value signalled by different sensory stimuli during sleep is not clear. On page 479, French *et al.*[4] show that the fruit fly *Drosophila melanogaster* also actively processes sensory information during sleep, and that the salience of different sensory stimuli can be affected by whether it is fed or starved.

Sensory processing during sleep can be studied in humans by repeatedly awakening participants and asking them to recall their most recent sensory experience before waking, while monitoring their brain activity[5]. Although such a 'serial awakening' approach cannot be used in other animals, sensory processing during sleep can be investigated in certain model animals using high-throughput behavioural analyses and approaches to manipulate the activity and gene expression of various populations of neurons.

A few years ago, researchers from the same group as French *et al.* developed an open-source robotic machine called an ethoscope that can deliver behaviourally triggered stimuli to flies in a feedback-loop mode, allowing high-throughput analysis of how sensory stimuli affect individual flies during sleep[6]. Using this machine, French *et al.* delivered sensory stimuli to each fly whenever they fell asleep, akin to the 'serial awakening' experiments typically performed in humans.

The authors assembled a panel of various odorants, and tested whether the sleeping flies woke up in response to each of the odorants delivered at different concentrations, and at different times of day and night. They found that sleeping flies were more likely to be awoken by odours that, when the insects were awake, they found aversive than by those they found attractive or neutral (that is, neither attractive nor aversive).

But when flies were starved before sleep, their responses changed (Fig. 1). Food odours, but not non-food odours, were more likely to wake the flies when they had been starved than when fed, suggesting that the odours were more salient to the starved flies. These findings suggest that flies process complex sensory information during sleep, and that their responses are modulated by their internal state. The results thus reveal a previously unknown feature of sleep in a non-mammalian model that is analogous to sensory processing in sleep by humans.

To identify the neuronal cells involved in this process, French *et al.* searched for cells that connect two parts of the fly brain involved in sleep: the mushroom body and the fan-shaped body[7,8]. The neurons that transmit information from the mushroom body have been comprehensively identified, and several tools are available to label and manipulate specific populations of these neurons[9,10].

French and colleagues identified two populations of neurons in a circuit that regulates arousability during sleep: neurons that carry output from the mushroom body, and their putative target neurons in the fan-shaped body. Blocking neural communication by either of these populations of neurons made flies more easily woken by odorants, suggesting that these neurons are active during sleep to prevent odour-triggered awakening.

Next, the authors found two sets of neurons that act to 'gate' the effects of starvation on the arousal evoked by food odours. The first set are olfactory neurons that detect odorants through receptor proteins expressed on the neuronal-cell surface. The other gating population of neurons releases the neurotransmitter molecule dopamine and forms synaptic connections with the output neurons of the mushroom body. Artificially deactivating either the olfactory neurons or the dopamine-releasing neurons stopped starved flies from being more easily aroused by food odours than by other odours. These findings suggest that the fruit fly, with a brain of only about 100,000 neurons, could be used to investigate how sensory processing differs between sleeping and waking states.

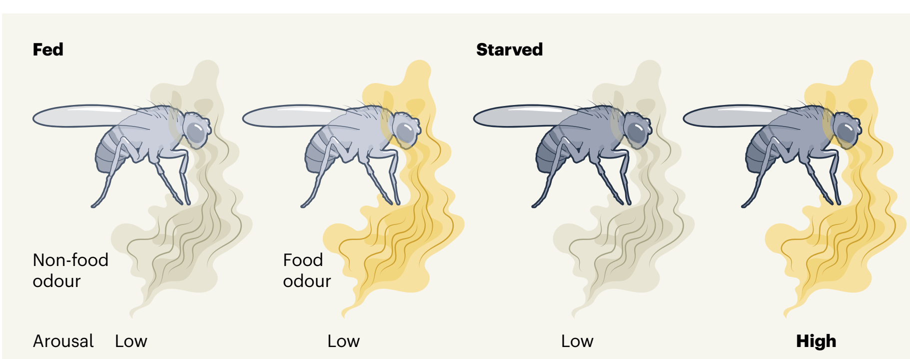

Figure 1 | A fly's internal state affects its response to sensory information during sleep. Using a machine called an ethoscope, French *et al.*[4] delivered various odorants to *Drosophila melanogaster* fruit flies when the insects were asleep, and tracked the flies' behavioural responses. The authors found that food odours and non-food odours awakened the flies at a similarly low rate. However, if the flies were starved of food, they woke up much more readily in response to food odours, but not to non-food odours. This finding implies that flies continue to process olfactory information, as well as the value attached to different odorants, during sleep.