control mice. However, in mice expressing the DT-receptor in peripheral neurons, the fusion toxin induced diarrhoea and colonic tissue damage. In addition, the authors show that the expression of the DT receptor in DRG neurons is sufficient for the fusion toxin to induce neurogenic inflammation in the gut and other hallmarks of CDI.

*Clostridioides difficile* exploits changes in the host's gut metabolism that occur during CDI to enhance its own proliferation and colonization[9]. Consistent with this, levels of *C. difficile* were reduced in mice lacking a functional copy of *Tac1* compared with those in animals with a functional copy of the gene. Similarly, in mice lacking a functional copy of the gene *Calcb*, levels of *C. difficile* were reduced compared with those in animals with a functional copy of the gene.

Finally, the researchers address the therapeutic implications of their findings. Selective NK1 receptor inhibitors, which block SP signalling, are available to counteract severe vomiting induced by anticancer drugs, for example. In addition, antibodies against CGRP (such as fremanezumab) or inhibitors of CGRP receptors (such as olcegepant) have been developed for the treatment of migraine. All of these drugs, the authors found, greatly reduced signs of disease in the case of TcdB gut injection and also in the CDI mouse model.

Although FZD receptors have a key role in infection mediated by many subtypes of TcdB, some hypervirulent strains of *C. difficile* exist, such as ribotype 027. These strains are characterized by the toxin TcdB2, which does not bind to FZD. However, the injection of TcdB2 and also TcdA induced footpad swelling that can be blocked by an NK1 receptor inhibitor, suggesting a crucial role for neurogenic inflammation regardless of the specific toxin subtype and receptor type.

This study fills a key gap in our knowledge of the disease underlying CDI and offers new perspectives on treatment options to explore. It is worth noting, too, that the experiments provide good support for previous findings[10] regarding the importance of SP for the effects mediated by TcdA.

Many questions remain unanswered. Investigating the precise role of intestinal pericytes is an exciting topic for future research. The question of why and how *C. difficile* toxins, which inactivate Rho proteins by glucosylation, prompt the release of SP and CGRP should be investigated. Understanding the interactions of the many toxin-sensitive cell populations in the gut over the course of toxin action remains a major challenge to address.

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Photonics

# The compact accelerator that confines as it drives

**Yelong Wei**

A silicon-based device uses laser light to accelerate electrons and simultaneously shape them into a narrow beam. The principle could be used to build microchip accelerators that do away with bulky conventional designs. **See p.476**

Whether they're used for cancer treatment or testing the fundamental tenets of physics, particle accelerators are designed to drive narrow beams of charged particles to extremely high speeds and energies — and they typically take up a lot of space. But what if these speeds and energies could be achieved on a microchip no bigger than a fingertip? One way to do so involves increasing the rate of energy transfer so that the particles can be propelled to high energies over very short distances. On page 476, Chlouba *et al.*[1] report an accelerator that can increase the energy of particles by 43% in just 500 micrometres. Realizing a

## From the archive

**Studies of behaviour grab the limelight, and Charles Darwin shares ideas about how organ loss might evolve.**

### 50 years ago

The award last week of a Nobel Prize to three animal behaviourists ... marks the full emergence of the study of animal behaviour from one of the less respectable corners of natural history to the forefront of the biological sciences.

**From *Nature* 19 October 1973**

### 150 years ago

My father finds that in his letter ... he did not give with sufficient clearness his hypothetical explanation of how useless organs might diminish, and ultimately disappear. I therefore now send you, with his approval, the following further explanation of his meaning. If one were to draw a vertical line on a wall, and were to measure the heights of several thousand men ... against this line, recording the height of each by ... a pin, the pins would be densely clustered about a certain height, and ... their distribution would diminish above and below ... Supposing ... that a race of cattle becomes exposed to unfavourable conditions, my father's hypothesis is that, whilst the larger proportion of the cattle have their horns developed in the same degree as though they had enjoyed favourable conditions, the remainder have their horns somewhat stunted ... If .. horns are useless organs, the cattle with stunted horns have as good a chance of leaving offspring (who will inherit their peculiarity) as their long-horned brothers. Thus, after many generations under the poor conditions, with continual intercrossing of all the members, the symmetry of distribution will be ... restored, but it will have come about through the general removal of *all* the pins downwards, and this will ... have shifted the central cluster. Thus, supposing the hypothesis to be supported by facts (and my father intends to put this to the test ...), there is a tendency for useless organs to diminish and finally disappear, besides those arising from disuse and the economy of nutrition. GEORGE H. DARWIN

**From *Nature* 16 October 1873**

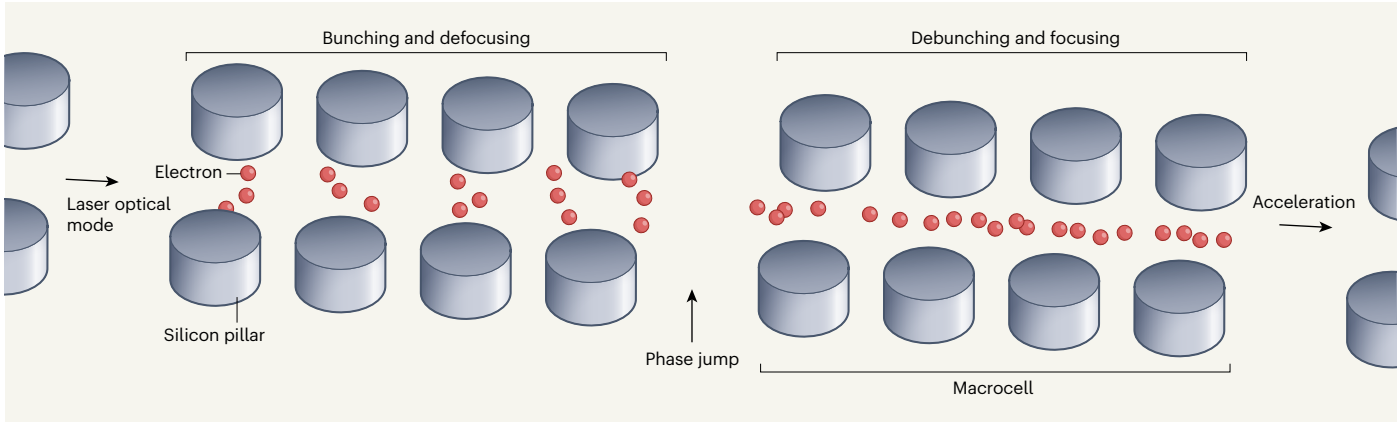


**Figure 1 | A structure that can simultaneously accelerate and confine a beam of electrons.** Chlouba *et al.*[1] designed a device that could be used in a compact alternative to conventional particle accelerators. A laser beam generates an 'optical mode' that accelerates electrons inside a structure fabricated from micrometre-scale silicon pillars. These are arranged in 'macrocells' that are separated by gaps designed to induce sudden changes in the phase of the light (the degree to which the light waves are in step with each other). Depending on the phase, the macrocells either bunch the electrons and defocus the beam, or focus the beam and debunch the electrons. This successive manipulation of the electrons by the macrocells produces a fast-moving, narrow beam.

fingertip-sized accelerator no longer seems like science fiction.

The first accelerator resembling a microchip appeared ten years ago[2], when a beam of electrons was accelerated with a 'gradient' (energy transfer rate) of 300 megaelectronvolts per metre (MeV $m^{-1}$) — an impressive rate, even for present-day accelerators. The device was made of silica glass and powered by a commercial laser beam, a set-up that is now known as a dielectric laser-driven accelerator (DLA). DLAs use the large electric fields from lasers to accelerate electrons with gradients that are up to 100 times greater than those achievable with conventional particle accelerators[2], opening a path to small, cost-effective accelerators. Subsequent DLA designs have achieved gradients as high as 850 MeV $m^{-1}$ for relativistic electrons[3] (which travel close to the speed of light) and 370 MeV $m^{-1}$ for subrelativistic electrons[4] (which travel slower than 90% of the speed of light).

But accelerators not only need to speed electrons up, they also need to confine them to very narrow beams. And this is challenging, because a principle known as Earnshaw's theorem[5] prevents bunches of charged particles from being focused simultaneously in all three spatial directions. Generally, external magnets are used to constrain electrons in a direction transverse to their motion, through a technique called alternating-phase focusing (APF). However, the submicrometre dimensions of DLAs make it difficult to use external magnets. In the absence of this type of confinement, the amount by which the electrons' energy can increase is constrained by their interactions with the laser pulses, and this limitation reduces the number of applications of DLAs.

An alternative approach, known as APF confinement, circumvents this problem by using the laser itself to confine the electrons (Fig. 1). The idea is that the laser light generates an 'optical mode' that moves along with the electrons, and this mode initially acts to accelerate the electrons. But the device is engineered with a set of micrometre-scale silicon pillars, arranged in blocks called macrocells, and the gaps between these macrocells are specially designed to induce sudden periodic changes in the phase of the light (the degree to which the light waves are in step with each other). These phase jumps have the effect of first focusing the electron bunches in a direction perpendicular (transverse) to their motion, thereby narrowing the beam, and then switching to focus them in the direction parallel to their motion to bunch them. Through such periodic switching, the limiting effects of Earnshaw's theorem can be overcome.

Members of the same research group as Chlouba *et al.* had previously demonstrated APF confinement in a silicon-based device that was 77.7 micrometres long, but the device did not accelerate the electrons[6]. Now, the group has implemented APF confinement in a tapered structure that succeeds in simultaneously accelerating and confining a pulsed electron beam. The macrocells that the pillars are grouped into alternately focus and defocus the electrons in the transverse direction. There are 25 gaps separating 26 of these macrocells, each of which is engineered to be different from the rest to take into account the increasing electron velocity.

By measuring the electrons' energy, the authors found that the particles behaved in a way that was consistent with their simulations of electrons interacting with laser pulses. The starting energy of the electrons was 28.4 kiloelectronvolts (keV), and the authors measured an increase of 12.3 keV, which corresponds to a gradient of 22.7 MeV $m^{-1}$. This gradient is comparable to the capabilities of modern electron accelerators[7]. Another group[8] has recently demonstrated a similar DLA that measures 708 micrometres in length and uses APF to achieve energy gains of up to 23.7 keV — a 25% increase from a starting energy of 96 keV.

Both experiments show substantial energy gains for subrelativistic electrons, demonstrating strong potential for compact DLAs and paving the way for the construction of microaccelerators in the future. However, some obstacles must be overcome before these devices can be realized. One of the most pressing issues is that the electron currents are very low after passing through a device measuring hundreds of micrometres. One approach to increase the current might involve introducing a second laser to create an interference pattern between the two lasers. This pattern is known as an optical beat note and can, in principle, compress electron pulses[9]. Incorporating an optical beat note will require yet another feat of engineering, similar to those reported here.

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