of neuron-to-neuron communication, controlling the release of neurotransmitter molecules[8,9]. Interestingly, Ma *et al.* and Brown *et al.* found that loss of nuclear TDP-43 led to mis-splicing of transcripts encoding several proteins involved in neurotransmission. This suggests that changes in the properties of neurotransmission might have a general role in ALS and FTD. But how changes in UNC13A-dependent neurotransmission might be involved is uncertain.

It has previously been hypothesized that UNC13A might contribute to neurodegeneration by boosting the release of the excitatory neurotransmitter glutamate, which is known to have toxic effects that can lead to neuronal death[2]. However, the current studies do not favour this scenario, mainly because UNC13A loss is expected to cause a decrease in glutamate release[8]. In addition, past work does not support the idea that UNC13A-mediated changes in neurotransmission would lead to neurodegeneration. Mouse mutants that completely lack UNC13A die at birth, but have a near-normal development of the nervous system[8,10,11], and mice harbouring mutated versions of UNC13A that lead to altered neurotransmission do not show signs of neurodegeneration[9].

One possible mechanism, and a probable focus for research in the coming years, is that it is the gradual loss of UNC13A in mature neurons that affects neuronal viability. But another, simpler mechanism could be considered. Neuronal loss prevents neurotransmission, and UNC13A loss is expected to have a similar effect[7] – the presence of neurons lacking UNC13A in people with ALS or FTD might have similar consequences to degeneration of neurons, for example promoting muscle loss.

Although many details remain to be resolved, the two studies raise an array of promising directions for research. For instance, might it be possible that the presence of mis-spliced *UNC13A* could assist in the diagnosis of ALS and FTD and in monitoring disease progression? Could UNC13A loss be relevant in other neurodegenerative conditions involving TDP-43, for example in some cases of Alzheimer's disease and Parkinson's disease[12]? Although beyond the scope of the current study, it is tempting to speculate on the potential of *UNC13A* as a therapeutic target for slowing disease progression and improving the prognosis of people who have ALS and FTD.

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Accelerator physics

Plasmas primed for rapid pulse production

Michael Litos

A plasma-based device is set to challenge particle accelerators that generate high-quality light pulses, with evidence that the cheaper plasma platform can run at competitive repetition rates. **See p.58**

Particle accelerators are usually associated with the discovery of fundamental particles, but they also have a long history of powering light sources. One such source is the free-electron laser, in which a high-energy beam of electrons from a linear accelerator generates ultrashort X-ray laser pulses by travelling through a series of magnets. However, conventional accelerators are expensive and unwieldy, needing up to one kilometre of space under Earth's surface, and a smaller, cheaper accelerator based on plasma (ionized gas) might be capable of doing the job. The plasma in such a device needs to settle before each new interaction with the electron beam, but the interactions must be repeated at a high rate to power a free-electron laser that has sufficient average brilliance. On page 58, D'Arcy *et al.*[1] report that the maximum repetition rate of a plasma-based accelerator could be as high as one million times per second – or even higher, putting it comfortably in the realm of nearly all potential applications.

> **"Because the plasma must be unperturbed for every shot of the electron beam, the recovery time of the plasma dictates the upper limit on the repetition rate."**

Although the specific demands of experiments using particle accelerators differ, the general themes remain the same. Namely, they require high-current, high-energy particle beams of extremely high quality. The quality of the beam is most simply quantified by the relative spread of the energy of the particles making up a single particle bunch, as well as the ability to focus the bunch to a small spot size – a quantity known as emittance. The beam current is the number of particles per bunch multiplied by the bunch repetition rate.

Maximizing the energy-use efficiency of the device and the energy gain of the particles while minimizing the spread of energies and increases in emittance has motivated much of the research on plasma accelerators over the past few decades, and there has been marked progress on these fronts[2–4]. The successful demonstration last year of a 27-nanometre-wavelength free-electron laser powered by an electron beam originating from a plasma accelerator represented a milestone for the field[5]. In the context of such advances, researchers have begun to turn their attention towards other topics that might allow plasma-based accelerators to move from basic research to application-ready technology. An experiment in 2020 demonstrated the relatively stable operation of a laser-driven plasma accelerator over many hours at a kilohertz repetition rate[6], representing another key advance.

But many applications require a repetition rate higher than kilohertz, so understanding the physical limitations associated with repetition rate is an area of ongoing investigation. To this end, D'Arcy *et al.* measured the recovery rate of a plasma source for an electron-beam-driven plasma wakefield accelerator. This type of accelerator uses an electron bunch to excite a density wave in a plasma that, in turn, increases the energy of a second, trailing electron bunch. Because the plasma source must be unperturbed for every shot of the electron beam, the recovery time of the plasma dictates the fundamental

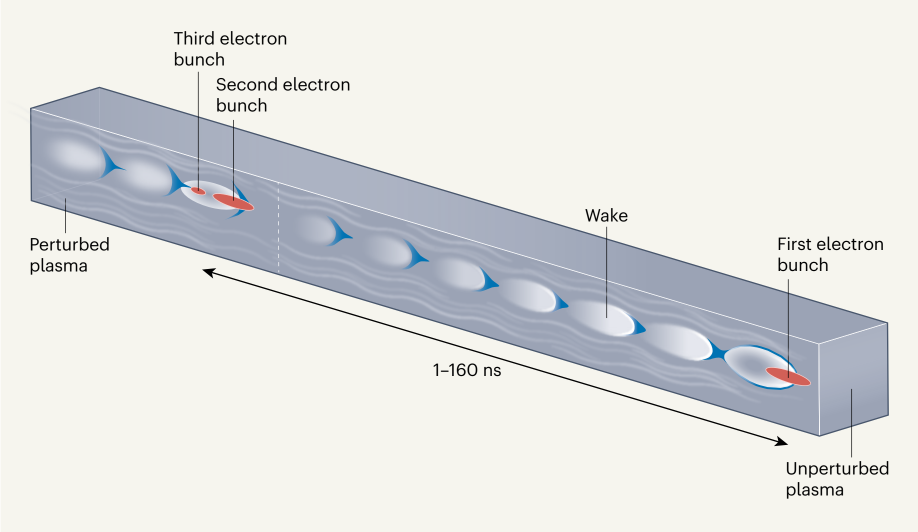

Figure 1 | Measuring recovery time in a plasma-based particle accelerator. Plasma wakefield accelerators are currently being developed as alternatives to conventional particle accelerators. In these devices, an electron bunch excites a density wave in a plasma (ionized gas), and the wave's wake is used to accelerate a second electron bunch to high energy. The wake varies from high electron density (blue) to low density (white). D'Arcy *et al.*[1] measured the recovery time of a plasma, which sets an upper limit on the rate at which bunches can be sent through the device. The authors sent a dense, high-energy electron bunch into an unperturbed plasma and, after a delay time of 1–160 nanoseconds, sent two more electron bunches into the same source, separated by hundreds of femtoseconds. The first bunch excited the plasma, and the second bunch created a plasma wake, in which the third bunch was accelerated. The authors inferred the state of the plasma on the basis of the behaviour of the accelerated electron bunch, and concluded that its recovery time was approximately 63 ns – corresponding to a repetition rate of around 10 megahertz, which readily meets the demands of future applications.

upper limit on the repetition rate.

The team used high-quality electron bunches with an energy of roughly one giga-electronvolt per particle. Three separate electron bunches were involved in each shot of the experiment: the first bunch was sent 1–160 nanoseconds ahead of the other two bunches to perturb the plasma by exciting a strong interaction similar to that in a plasma wakefield accelerator (Fig. 1). The other two bunches were sent in as a pair to test the response of a real plasma wakefield accelerator in the perturbed plasma source. One of these two bunches drove a strong plasma wake and the other, trailing only a few hundred femtoseconds behind, was accelerated by the wake. D'Arcy *et al.* adjusted the separation time between the plasma-perturbing bunch and the pair that followed, and in doing so, were able to emulate the behaviour of a plasma wakefield accelerator operating at repetition rates ranging from roughly 10 MHz to 1 GHz.

By measuring the final energy and divergence of the accelerated bunch as it exited the plasma, the authors ascertained the average plasma density encountered by the pair of bunches as a function of their relative delay with respect to the plasma-perturbing bunch. Using these data, they mapped out the time dependence of the plasma recovery process following the sort of strong perturbation associated with plasma wakefield acceleration. They found that it agreed well with a simple model of ion motion in the perturbed plasma. The reported experimental results show that the plasma had recovered to a state of uniform density after approximately 63 ns. Experiments in which pairs of electron bunches are separated by such a recovery time could achieve a maximum repetition rate of tens of megahertz or more.

These results provide some optimism for future applications of plasma wakefield accelerators. But other obstacles must be overcome before megahertz repetition rates can be achieved in practice. One of the most pressing issues is the residual heat deposited in the plasma after the passage of the electron beam. This heat will presumably need to be removed both rapidly and efficiently, presenting a major engineering challenge. One approach might be to incorporate supersonic gas flow transverse to the direction of beam propagation. However, such ideas remain speculative and will require further exploration.

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From the archive

A look at two books for travellers, and success reported in the effort to preserve a Stone Age monument.

100 years ago

Hints to Travellers. Scientific and General. By E. A. Reeves; *Camping and Woodcraft: A Handbook for Vacation Campers and for Travellers in the Wilderness.* By H. Kephart — Both these books are written for the traveller, but ... from different points of view ... The first may be said to minister to ... intellectual needs ... the second to ... material wants. "Hints to Travellers" ... has been known for many years as an almost indispensable volume for the traveller who aims at doing any useful scientific work. Mr. Reeves's volume on surveying and practical astronomy must have found its way into more remote corners of the world than any other book except the *Nautical Almanac* ... The addition of a few pages devoted to marine invertebrates would not be amiss in the natural history section, and might help to direct attention to an aspect of collecting which many travellers are prone to overlook ... Mr. H. Kephart ... devotes much attention to the growing class of holiday-makers who camp, not from necessity, but by choice ... The chapter on camp cookery is most elaborate ... [H]is dishes and recipes take us far from the simplicity of oatmeal, bacon, and tea, which are so often the staples of camp life.

From *Nature* 2 March 1922

150 years ago

We alluded some time since to the threatened destruction of one of the most notable megalithic monuments in this country, the Great Circle at Avebury, in Wiltshire. All archaeologists will be glad to hear that Sir John Lubbock has added one more to his eminent services to science by the purchase of the site on which the Circle stands ... [P]raise should be awarded to ... residents in the district ... who have ... shown their sense of the value of the monument, which is one of the glories of their county ... It is to be hoped that their example will stimulate similar zeal for the preservation of monuments in other parts of the country.

From *Nature* 29 February 1872