PLASMA PHYSICS

On the crest of a wake

Robert Bingham

What a conventional particle accelerator needs kilometres to achieve, a compact 'plasma wakefield' accelerator has just mastered in less than a metre. So is it adieu to the era of the gargantuan mega-accelerator?

Wakes — the areas of fluid turbulence most commonly seen around the pontoons of bridges and behind moving boats — have long excited human curiosity. Leonardo da Vinci carried out some of the first scientific investigations into wakes in the early sixteenth century by placing obstacles in fast-moving water (Fig. 1). During the 1830s, the Scottish naval engineer John Scott Russell noted that, at certain speeds, a boat travelling along a canal is actually accelerated by its own wake.

On page 741 of this issue, Blumenfeld et al.[1] take the exploitation of this wake effect to a new, higher-energy plane. They describe a technique for accelerating electrons in the wake of an ultra-relativistic electron beam propagating through an ionized gas (a plasma). Over a distance of less than a metre they succeed in doubling the energy of the electron beam at the Stanford Linear Accelerator Centre (SLAC) in California — which reaches 42 gigaelectronvolts (GeV) only after passing 3 kilometres of conventional technology based on radio-frequency accelerator cavities.

The result clearly demonstrates that the ultra-high gradients of 'plasma wakefield accelerators', which have previously operated[2–7] on scales of millimetres to centimetres, can be extended, in a metre-scale plasma, towards the high-energy frontier. That frontier currently lies at about 115 GeV, the energy achieved by the 27-km-circumference Large Electron–Positron (LEP) collider at CERN, the European particle-physics lab near Geneva, in its final

days in 2000 before it was dismantled to make way for CERN's new Large Hadron Collider. What's more, as the authors show, there is no fundamental barrier to extending high-gradient plasma accelerators to work over arbitrarily long distances.

In a conventional accelerator, the accelerating radio-frequency electric field is limited to the 'breakdown field' at which it begins to rip electrons from the surrounding metal (often superconducting) accelerator cavities. But a plasma is already broken down, which means that it can support electric fields orders of magnitude higher than can conventional accelerators. In the SLAC experiment[1], the factor is at least 1,000; correspondingly, the plasma is more than 1,000 times shorter for the same energy gain than the conventional part of the accelerator.

Plasma wakefields can be created by either a single, intense laser or by a particle beam. Last year, laser-driven wakefield accelerators were used to produce monoenergetic electron beams in the gigaelectronvolt energy range over a few centimetres[6]. Blumenfeld and colleagues' accelerator[1] is driven by the tightly packed relativistic electrons of the SLAC beam entering a metre-long column of lithium vapour (Fig. 2). The intense electric field of the beam immediately strips the electrons from the gas with such force that they are blown outwards in all directions, leaving behind the more massive lithium ions. To restore charge neutrality to the plasma, the displaced electrons snap back away

from the forwards-moving pulse, overshooting their original positions.

This oscillation in the plasma's electron density creates an oscillating electric wakefield, much like the wake produced by the boat in John Scott Russell's experiments, that accelerates part of the beam that formed it. Although the core of the electron pulse loses energy in setting up the intense plasma wakefield, the wakefield accelerates a small number of the electrons from 42 to 85 GeV over a distance of just 85 centimetres. A previous experiment[5] had achieved an energy gain of 2.7 GeV in a 10-centimetre-long plasma of similar density.

The SLAC experiment clarifies that an electron pulse can indeed propagate stably in a dense plasma for long distances without breaking up. No transverse deflections — 'sloshing' or 'hosing'[8] caused by the focusing effect of the ion column left behind by the passage of the electron beam — were observed. Hosing instability amplifies any asymmetry in the head-to-tail alignment of the beam, making directing the beam very difficult in longer systems. The lack of hosing also reduces 'betatron' emission, which occurs when electrons off the beam axis are attracted by the ion column, and wiggle back and forth across the axis emitting X-rays[9].

The maximum energy achieved in Blumenfeld and colleagues' experiments is determined by the expansion and consequent erosion of the beam head. The foremost part of the ionizing electron beam is not subject to the transverse focusing forces of the trailing ion column; the electric field of these electrons thus falls below the threshold for the formation of the plasma. This limiting effect can be overcome by higher-quality beams, in which electron spreading occurs only over distances much greater than the length of the plasma column.

Although these results are encouraging, current accelerator technology based on radio-frequency cavities is very successful, and has 50 years of development behind it. Replacing existing technology, wholly or in part, with plasma-wakefield acceleration will require further long and sustained effort. Maintaining high accelerating gradients over long plasmas is just one of a number of steps that need to be achieved. Particle colliders also require beams with an energy spread much smaller than that achieved by Blumenfeld et al.[1]. One way of achieving such a 'monoenergetic' beam is to boost the energy of a distinct second bunch trailing the drive bunch that sets up the wakefield — the afterburner concept[10]. Such a concept could be incorporated into a hybrid machine in which current mature technology produces an energetic beam up to 100 GeV, and the plasma accelerator takes it up to energies in the teraelectronvolt range over several metres.

Another essential ingredient of a collider is a counter-propagating positron (anti-electron) beam. Positrons have been accelerated in the wakefields of lower-density

Figure 1 | Turbulent history. A rigid obstacle in flowing water creates wake turbulence, a fact noted and sketched by Leonardo da Vinci in 1509. The passage of a moving body through a static medium has the same effect, and the turbulence can be used to accelerate a following body. What is true for a boat in water also applies to electrons passing through a gas, a fact exploited by Blumenfeld et al.[1] in their high-energy plasma wakefield accelerator.
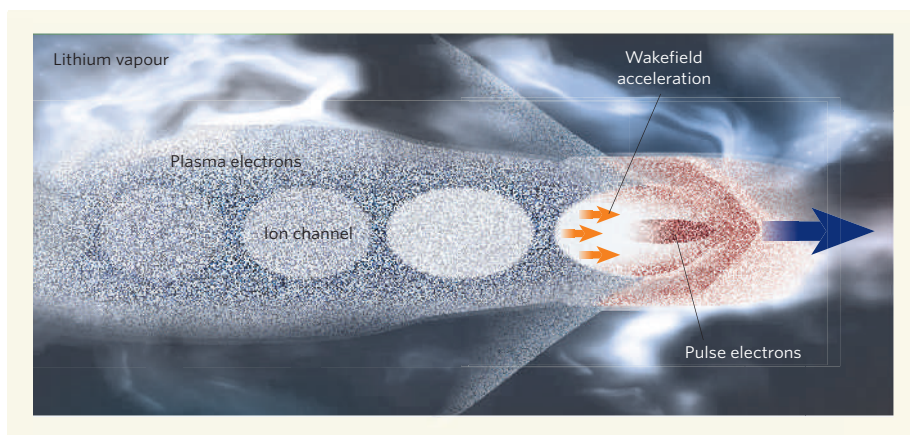
Figure 2 | Strip and surf. In Blumenfeld and colleagues' experiments[1], the 42-GeV Stanford Linear Accelerator electron beam ionizes lithium vapour with such force that it strips off all the atomic electrons, leaving only lithium ions behind. Most of the electrons lose energy in setting up the wakefield, but a small fraction are caught up in it and are hugely accelerated, doubling in energy over a path of just 85 centimetres.

plasmas with modest energy gains[11]. Such beams will also need to be focused down to nanometre-spot sizes, perhaps using the transverse fields set up within a 'plasma lens'[12]. Efforts in these areas will receive a welcome boost in the wake of Blumenfeld and colleagues' work, which has brought electron plasma-wakefield accelerators to the energy frontier that was previously the undisputed territory of large-scale particle accelerators. ∎

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VASCULAR BIOLOGY

Vessel guidance

Thomas Gridley

Embryos and tumours use the same signalling pathways to direct the formation of blood vessels. Discovery of a new role for the Notch pathway in that process presents a fresh option for cancer treatment.

Angiogenesis, the growth of new blood vessels from existing ones, is a highly active process in embryos. In adults, blood vessels in most organs are quiescent — except, notably, during the growth of solid tumours, when embryonic signalling pathways direct new blood vessels to grow around and into the tumour. Two players in this process are the vascular endothelial growth factor (VEGF) and Notch signalling pathways. Seven recent papers[1–7], including two on pages 776 and 781 of this issue[3,4], have yielded insights into Notch function during the formation of blood vessels in both embryos and tumours, and have revealed a new drug target for disrupting tumour angiogenesis.

VEGF is a secreted glycoprotein that is a potent inducer of angiogenesis both in embryos and in tumours[8,9]. The Notch pathway is an intercellular signalling system in which both the signalling (ligand) and receiving (receptor) molecules are anchored to the cell surface, thereby restricting signal transmission to cells that are physically adjacent. This pathway is frequently involved in regulation of cell differentiation, and previous work[10–12] had shown that the Notch ligand Delta-like 4 (Dll4) is essential for vascular development in mice. The new studies[3,4] identify a previously unknown role for Dll4/Notch signalling during vascular development, and clarify the mechanism responsible for the vascular defects that result from reduced Notch signalling.

The various groups analysed blood-vessel development in three different experimental systems: the zebrafish embryo[4,7], the retina of the mouse eye[2,3,5,6], and solid tumours growing in mice[1,2]. Developing zebrafish embryos are almost transparent, making them ideal for high-resolution imaging studies of blood-vessel development. The advantage of the mouse retina is that blood vessels develop mainly after birth in a highly reproducible spatial and temporal pattern; during these stages, the retinal vasculature is accessible both for observation and for experimental administration of drugs or other agents.

A finding common to all the studies[1–7] was that inhibition of Notch signalling led to increased sprouting and branching of blood vessels. The Notch pathway regulates sprouting and branching behaviours by influencing the formation of vascular 'tip cells' — specialized endothelial cells at the leading edge of vascular sprouts. The tip cells extend protrusions, called filopodia, that sense the local environment and guide growth of these sprouts along gradients of VEGF protein. In both the mouse retina and the zebrafish embryo, Dll4/Notch signalling regulated the formation of tip cells. Reduced Notch signalling led to increases in the number of tip cells, extension of filopodia and branching of vessels (Fig. 1). Conversely, pharmacological or genetic manipulations that blocked VEGF function reduced both Dll4 expression and blood-vessel sprouting[2,4–7], indicating that the suppression of tip-cell formation and angiogenic sprouting by Notch signalling occurs downstream of the VEGF signal.

Growth and metastasis of solid tumours require the recruitment of host blood vessels. Many solid tumours express the angiogenesis-promoting VEGF, and anti-VEGF therapies are effective in blocking growth of solid tumours in rats and mice[9,13]. Notch signalling is essential for angiogenesis in embryos[10–12], but does not seem to have a major role in maintaining established blood vessels in adults. So protein components of the Notch pathway, particularly if their expression and function are confined to the vascular system, may provide drug targets during tumour angiogenesis.

Two of the studies[1,2] have identified the Dll4 protein as just such a drug target. Systemic administration of either neutralizing antibodies against Dll4, or a recombinant form of the Dll4 protein that had been modified to block Dll4/Notch signalling[1], inhibited growth of several different solid tumours in mice. As with the findings in zebrafish embryos and mouse retinas, anti-Dll4 treatment increased the sprouting and branching of blood vessels, and led to a marked increase in blood-vessel density in tumours. But tests of the vascular network in these tumours revealed that the new vessels functioned inefficiently and were not connected functionally to the vascular network of the tumours, leading to an overall inhibition of tumour growth (Fig. 1).

Unfortunately for many patients with cancer, individual therapies can be ineffective against specific tumours, and tumours that respond initially to drugs can become resistant to them. In these studies[1,2], anti-Dll4 treatment inhibited tumour growth better when combined with anti-VEGF treatment than when given