ensures that the flow within the pipe remains streamlined and rapid (an extra benefit is suppression of the jet break-up as it leaves the nozzle). This is one of the few known practical applications of elongational viscosity, as opposed to the widespread use of polymers to increase shear viscosity, such as the thickening of foodstuffs by starch, a naturally occurring polymer. So it is intriguing, as noted by Bergeron *et al.*, that the same elongational viscosity should act to reduce rather than increase flow, thereby suppressing the rebound of water droplets.

To confirm their theory, Bergeron and co-workers[4] show that drops of a polymer solution with a high extensional viscosity retract at the same speed as drops of polymer-free water thickened to the same high viscosity by mixing with glycerol. Such evidence is circumstantial but persuasive: the implication is a new and unexpected demonstration of extensional viscosity, and may find applications in other areas where rapidly deforming thin films are involved. An extra bonus of this system, as the authors point out, is that the shear viscosity of their dilute solutions remains almost indistinguishable from that of pure water, ensuring that little viscous friction is encountered while handling and pumping the liquids. The high elongational viscosity becomes important only when it is needed — during the rapid deformation of the retracting drop. Not an intelligent liquid, perhaps, in view of its simplicity, but certainly a smart one. ■

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Neurobiology

Nervous engineering

Melitta Schachner

The ability to repair damaged tissue in the human nervous system has long been a goal of neurobiologists. Writing in *Proceedings of the National Academy of Sciences*, Todd Holmes and colleagues[1] describe a promising biomaterial for this purpose. It consists of a peptide scaffold that can act as a substrate for the attachment of neurons, and allows the growth of nerve fibres and the formation of synapses — the specialized connections between neurons. It is early days as yet, but the idea is that such artificially grown tissue could be transplanted into patients.

Repairing nervous tissue is no easy task. Cell replenishment happens in many other adult mammalian tissues, but very few new neurons are produced in the adult central nervous system. Moreover, the outgrowth of fibres from regenerating neurons into damaged areas is controlled by various molecules that can promote or inhibit the process; and neurons that lack an appropriate substrate cannot regrow and are vulnerable to self-destruction through apoptosis. An ideal transplantable substrate for repairing damaged tissue in the nervous system should support neuronal attachment, fibre outgrowth, and survival and formation of active synapses. Such a substrate should be well tolerated *in vivo*.

Development of the new peptide-scaffold biomaterials[1] started with a serendipitous observation by Holmes and Shuguang Zhang, another of the authors on the paper. Holmes was testing the neurotoxicity of peptides in neuronal cultures, and Zhang provided him with the so-called EAK16 peptide for the purpose. As its name implies, EAK16 is 16 amino acids long, and it is made up of repeating units of negatively charged glutamate residues (E in single-letter amino-acid code) and positively charged lysines (K), separated by hydrophobic alanines (A). This arrangement gives EAK16 two distinct polar and non-polar surfaces.

Much to their surprise, Holmes and Zhang observed the formation of macroscopically well-ordered, thin-sheet structures in the neuronal cultures into which EAK16 was introduced; moreover, there was no measurable neurotoxicity in the cultures exposed to the peptide. They went on to find out that the formation of the macroscopic sheet structures from EAK16 depended on millimolar levels of monovalent salts. Scanning electron microscopy of the sheet structures revealed a fibrous assembly of the EAK16 material. The openings between the microscopic fibrils were small enough to exclude cells, but large enough to allow the passage of macromolecules. Holmes, Zhang and colleagues devised a molecular model for the salt-induced formation of the EAK16 material and published their findings in 1993 (ref. 2).

The sequence of EAK16 has some similarity to the RGD (arginine-glycine-aspartate) sequence that is characteristic of some integrin receptors, molecules that are central players in cell adhesion and nerve-fibre outgrowth. On making the EAK16 derivatives RGD16 and RAD16, Holmes and Zhang found that the RAD16 peptide formed stable macroscopic sheets in solutions containing salt at physiological levels. In contrast, no macroscopic materials were formed from the RGD peptides. With the help of Michael DiPersio, they tested the hypothesis that cells would attach and grow on the RAD16 peptide biomaterials in an integrin-dependent fashion. They found, however, that both EAK16 and RAD16 peptide biomaterials robustly supported the attachment and growth of many types of non-neural primary

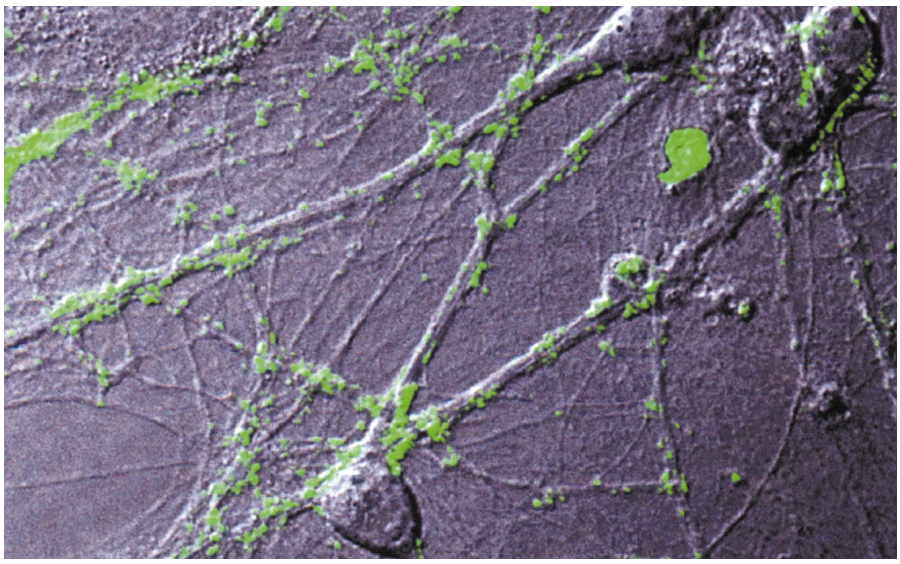

Figure 1 **Synaptic activity of neurons grown by Holmes *et al.*[1] on their peptide scaffolds. The neurons concerned come from rat hippocampus; the fluorescent dye is indicative of neurotransmitter release. (Reproduced from ref. 1.)**

and transformed cells[3]. Many of the cell types completely colonized all surfaces of the peptide-based sheet biomaterials, giving the appearance of tissue.

Remarkably, the new paper[1] shows that these peptide biomaterials also support neuronal survival. Robust networks of nerve fibres grew from both primary neurons and neuron-like transformed cells on the RAD16 scaffold, and to a lesser extent on the EAK16 scaffold. Furthermore, the neurons formed functional synapses, as shown by labelling with a fluorescent dye that was taken up into vesicles following neurotransmitter release at synapses (Fig. 1). There were no immunological or inflammatory reactions when the peptides were injected into rat muscle.

Inflammatory reactions in muscle and brain are quite different, however. So these peptide-based biomaterials will have to succeed in tests of how well they are tolerated in brain, spinal cord and peripheral nerves if they are to be useful for repairing damaged nervous tissue. (Preliminary results, which show that they do not elicit a significant adverse cellular reaction when introduced into brain, provide cause for optimism; T. Holmes and colleagues, personal communication.) Beyond that, we now know of numerous receptors and ligands that mediate neuronal attachment, survival, nerve-fibre outgrowth, synapse formation and modification of synaptic strength. The incorporation of such molecular cues into the peptide scaffolds would be necessary to add further specificity for the attachment and directed outgrowth of particular neurons and nerve fibres. Finally, thorough animal trials with different types of acute and chronic neural damage would have to be carried out before even contemplating trying this approach in humans.

Clearly, the aim of repairing a damaged nervous system remains a long way off. But the further development of biological materials, and the possibility of combining them with cell-based therapies, may bring us closer to realizing that goal. ■

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Mathematics

Curves and numbers

Ivar Ekeland

The most resounding achievement of mathematics in the twentieth century may well have been the proof of Fermat's last theorem. As readers of *Nature* may be aware[1], Pierre de Fermat stated this result in the margin of a treatise by the Greek mathematician Diophantus, along with the remark that he would write the proof somewhere else, because the margin was too small to contain it. That proof has been missing for three and a half centuries, if it ever existed, and in 1993 Andrew Wiles finally supplied a different one, using methods way beyond anything Fermat could have known[2]. Wiles' solution involved a partial proof of another difficult problem, known as the Shimura–Taniyama–Weil conjecture, and this conjecture has finally been proved in full by Christophe Breuil, Brian Conrad, Fred Diamond and Richard Taylor[3].

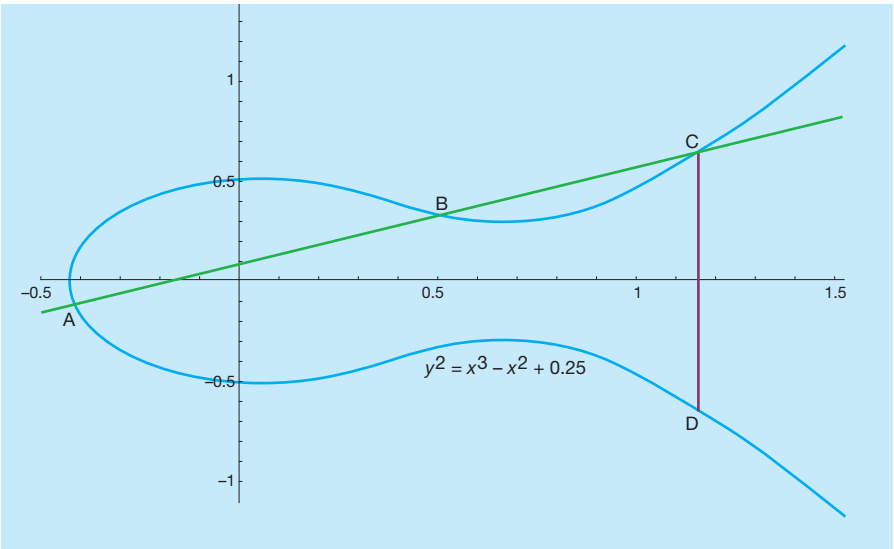

Figure 1 **An elliptic curve of the form $y^2 = x^3 - x^2 + 0.25$. What makes elliptic curves worth studying is their natural group structure. The group operation follows from connecting points A and B by a straight line, projecting the line to find a third point C, and then reflecting this point about the *x*-axis to give point D. Andrew Wiles proved Fermat's last theorem by studying a particular elliptic curve, which involved a partial proof of the Shimura–Taniyama–Weil conjecture. This conjecture has been proved in full by Breuil, Conrad, Diamond and Taylor[3,4].**

Fermat's theorem states that, for any $n \geq 3$, the only integer solutions of the equation $a^n + b^n = c^n$ are the obvious ones, where a, b or c are 0. For $n = 1$ there are, of course, many other solutions, and for $n = 2$ we have the solution $a = 3$, $b = 4$ and $c = 5$ (a rectangle triangle with integer sides). That such solutions don't exist for higher values of n is surprising, but it is tempting to think that the problem would yield to a bit of smart algebraic manipulation. It does not: generations of amateur mathematicians have tried to do it this way, and failed.

The breakthrough came from another direction: the theory of elliptic curves. These are curves in two variables, x and y, defined by a cubic equation of the form $y^2 = x^3 + px + q$. They can be plotted as points in the x–y plane (Fig. 1), and they have remarkable properties that have captivated mathematicians for centuries. Let me quote just one of them: an elliptic curve has a natural group structure. Group theory is the mathematics of symmetry, and a mathematical group is just a set of elements that can be combined together in pairs to yield another element of the set.

For an elliptic curve (Fig. 1), this group operation is defined geometrically. Given two points A and B on the curve connected by a straight line, the straight line will intersect the curve at a third point C (because the equation defining the curve has degree three). If the curve is reflected about the x-axis, the curve itself remains unchanged, but the point C is changed to point D. As a function of A and B, point D obeys a group law that requires operations to be associative — that is, A(BD) = (AB)D. There are two other algebraic laws that define group structure: the existence of the inverse of any element, and the existence of an identity element. Both of these are true of elliptic curves.

Fifty years ago, Shimura, Taniyama and Weil conjectured that all elliptic curves would be 'modular' — a property described in Box 1. In mathematics, a conjecture is something that is believed to be true but is still waiting for a proof. Interest in the Shimura–Taniyama–Weil conjecture was rekindled in 1996, when Gerhard Frey and Ken Ribet observed that if integers a, b and c