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Micro scalpel offers unprecedented precision

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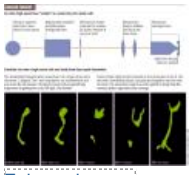
CUTTING things up to see how they work has a long, if gruesome, tradition in medicine. In the UK, early anatomists sliced open the corpses of executed criminals and grave-robbed cadavers to get a look at what was inside. Others performed surgery on living animals - slitting here, removing an organ there - to figure out which parts were vital, which merely useful, and what they all did. Thanks to these knife-wielding researchers, we know volumes about how the body works - but only down to a certain level.

At the microscopic scale, it's a different story. The cooperative workings of nerve cells, say, or the capillaries in the brain, are largely mysterious. Our knives are too crude to work on such tiny things. What if we had a scalpel small enough to dissect this micro world?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Cellular surgery

Wish granted. A new tool for performing delicate surgery on individual cells is opening up a new biological world. It can precisely cut or remove parts of a cell without killing the cell itself. With its help, we can measure the tension and elasticity of a cell's own framework - features that can cause disease when they go wrong. We can unravel mysteries about the intricate and dynamic network of molecules inside cells that governs their behaviour and often breaks down in illnesses such as cancer. What's more, this micro scalpel is already giving new insights into the mechanics of the motors that allow bacteria to swim and the ways that nerve cells can repair themselves. "Now we can begin to look at the functions of individual molecules in the physical context of where they operate in the cell," says Donald Ingber, a cell biologist at Harvard Medical School and Children's Hospital Boston.

> “For the first time, people had operated on a living cell without damaging or killing it”

This minuscule scalpel takes the form of a femtosecond laser, a device that can vaporise cell structures with a precision of a couple of hundred nanometres or less. Of course, lasers are nothing new in surgery: they have been used for several decades to cut biological tissue, and are well known in eye surgery. But the femtosecond laser is in a different class. First, the beam can be tightly focused on an area about a tenth that zapped by other lasers. Moreover, rather than burning off surface tissue, it can target a point inside a cell or under the skin - leaving the outer layer and surrounding areas undamaged. "The beauty of the femtosecond laser is that it only affects the focal area, and it gets below the surface," says David Kleinfeld, a biophysicist at the University of California, San Diego.

Laser sharp

The key feature of the femtosecond laser is this: it shoots extremely short pulses of light and it does so thousands of times a second. Each shot lasts only 10 to 100 femtoseconds - 10^{-14} to 10^{-13} seconds - but

produces a spot as hot as the sun in its target material. Between pulses much of that heat dissipates, so it doesn't build up and damage surrounding tissue. In the end, the target material turns into a plasma of electrons that boil off, but leave a tiny amount of dust. "It's a very efficient process. Almost all the energy goes to ablate the material," says Adela Ben-Yakar, an engineering physicist at the University of Texas at Austin.

In the early 1990s, Harvard University physicist Eric Mazur began using a femtosecond laser to trigger tiny explosions inside glass, with the aim of creating cavities that could be used for storing data. But by the end of the decade, he had realised that the device might also be used to blitz structures inside cells and tissues. In 2000 Mazur's physics group teamed up with Ingber's cell biology group and began shooting the femtosecond laser at targets in cells. And sure enough, they found they could wipe out a single mitochondrion - the organs within a cell that generate` its energy. No one had ever done this before, but the achievement was more impressive still: the team also managed to knock out a mitochondrion without bursting the cell's outer membrane, damaging other mitochondria in the same cell or killing the cell itself. For the first time, people had operated on a single living cell.

That demonstration opened up the possibility of manipulating biological systems at a scale that had been mostly off-limits before. At present, most scientists' finest tools - the needles used in microsurgery - are too bulky for working with any but the largest of cells, such as egg cells. Even then, a high proportion of cells don't survive the operation. Other ways of knocking out cell structures or functions, such as chemicals or gene mutations, can often only target whole cells, or are not very controllable or precise in their effects. The femtosecond laser, on the other hand, can zero in on a single structure just 100 nanometres to 10 micrometres across - the realm of organelles, single cells, bacteria and simple tissues.

Now a handful of research groups are trying out the device. Ingber, for example, is training the femtosecond laser on the cytoskeleton - the intricate protein scaffold that holds up every cell. But it is more than a simple support: tugs on one part of the cytoskeleton not only change the cell's shape but can also trigger signals that affect its physiology. Defects in this system, known as mechanotransduction, play a role in diseases such as hypertension, arthritis and emphysema.

Ingber's team uses a traction force microscope to measure the tension on a cell's cytoskeleton fibres and the femtosecond laser to snip individual fibres. So far, Ingber says, he's been surprised to find that a change in the tension of a single fibre can cause one kind of molecule to alter its chemical reactivity while another type of molecule nearby remains unchanged. What's more, snipping a single fibre - one of many thousands in the cell - can alter a cell's entire shape.

Biophysicist Howard Berg of Harvard University is hoping for similar success in probing the mechanics of the molecular motor that powers the well-known gut bacterium *Escherichia coli*. Although *E. coli* is probably the best understood free-living creature on the planet, biologists still don't know how its tiny rotary motors manage to drive the four or five whip-like tails or flagella that spin clockwise and then anticlockwise, propelling the bacterium in search of food. They know a lot about the chemical receptor system that triggers *E. coli* to move in a certain