SCIENCE

Learning from the motors that cruise a cell's highways will have revolutionary consequences, says **Roger Highfield**

# This is what drives you

AS YOU read these words, tiny motors are guiding your eyes precisely across the page. Others are whirring within your brain to enable you to think about this sentence. Many more are getting on with the serious business of life itself, delivering heart beats, digesting food and driving metabolism.

Each one of your cells can be thought of as a metropolis within which these motors trundle about. Millions dart hither and thither along the cellular equivalent of roads at speeds approaching 18 millimetres per hour.

They come in more shapes and styles than the cars in London: some go ''forward'', some ''backwards''. Others glide and skip. There are even some that do cartwheels. They stop, start, speed up and slow down in response to still unknown traffic signals.

Amid this bustle, motors hold the cell in shape, orchestrate the movement of genetic material — DNA — and help import nutrients and export wastes. Others lug packages of messenger chemicals along nerves.

During cell division, the network of routes is rebuilt, leading scientists to suggest that some anti-cancer drugs work by blocking the essential road works that enable a cell to divide in two. And just as gridlock can paralyse a city, so pot holes in a cell's roads and faults in the motors can halt a heart, disrupt the brain, or ruin the body plan of a developing embryo.

A detailed portrait of the workings of molecular motors was given last month by two pioneers in the field, Prof Ronald Vale of the University of California, San Francisco, and Prof Ronald Milligan of the Scripps Research Institute, La Jolla.

''As we learn more about these molecular motors they have become more familiar and less magical,'' they said in the journal *Science*. And yet much of the mystery remains, notably in the awesome efficiency of these motors and the way they are customised for each use.

Researchers have used X-rays, lasers and electron microscopes to study molecular motors. They have identified the shapes and sizes of their components. They have labelled the parts with clusters of gold, balls of rubber and beads of silica to show how they bend, deform and move during their labours.

But if you could lift up the ''bonnet'' of a molecular motor and peek inside, you would not find anything even remotely resembling a car engine, let alone spark plugs or other familiar components.

The motors are proteins, which consist of long strings of amino acids, arranged in sheets, spirals (helices) and other complex shapes. Some parts are rigid, others bend and a few are designed to catalyse chemical reactions.

Just as a car's engine burns petrol to push the vehicle along, molecular motors harness energy from chemical reactions. The petrol is a ubiquitous molecule called ATP.

Within a fluid-filled cell, the motors receive a machine gun battering by molecules of all sorts and, at random, they will bind to an ATP fuel molecule. The ATP reacts with water to make ADP, which remains stuck to the motor for a time before being stripped off. Each step in this chemical sequence triggers a change in the motor's shape.

The motors that cruise the cell's highways come in three families. The first, known since 1864, is myosin, which makes muscle contract along rails of actin filament.

The second, known since the early 1960s, is dynein. This cumbersome motor rattles along microtubules, flaps the fronds (cilia) that motivate microorganisms, and links microtubules in the tails of sperm, enabling them to wriggle. Because of its large size, dynein has been difficult to study.

The third, kinesin, was purified by Prof Vale in 1985. This transports packages around inside cells — including nerves — on rails called microtubules, and plays a central role in cell division.

FIVE years ago these three motors looked very different. Now two of the three — myosin and kinesin — are beginning to look very similar.

They were originally put in separate families for good reason. There are no similarities in their associated genetic sequences, which describe the amino acid sequence within each protein. The business end of kinesin is less than half the size of myosin's and seems to work differently: when fuel binds to kinesin, it drives the power stroke. Yet this same step makes myosin release a muscle fibre.

The movements are different: myosin fibres reach out to grab the actin in muscle, rather like out-of-time rowers in a boat. Two ''feet'' at the end of the myosin skip along the actin, propelling it in the process, with a motion that resembles two fingers in a ''come hither'' gesture.

In contrast, kinesin has two feet that waddle along the vertebrae-like sections of a microtubule. As the ATP docks, one foot swings out and flaps about before latching on to the next vertebra. Recently, however, Prof Vale has found that myosin and kinesin share a core mechanism that converts chemical energy into movement, rather like internal combustion engines contain common components such as pistons and crankshafts.

''The big message is that myosins and kinesins are a good example of nature's innovation: evolution has taken a single fundamental mechanism and elaborated on it to come up with a wide range of molecules with very different attributes,'' said Prof Milligan.

The first clue came in 1996, when Prof Vale and Prof Robert Fletterick of University of California, San Francisco, produced the first X-ray picture of the kinesin protein. Despite the fact that the genetic codes for kinesin and myosin are so different, ''the central parts of these motors, where the ATP is, were very similar,'' he said. ''You could overlap the structures on a computer and they superimposed beautifully.''

Within this common core ATP fuel is burnt to release phosphate (chemical energy) and generate a movement, as the motor changes shape. The core drives the motor using two loops of amino acids.

When the phosphate arrives, one loop swings like a gate. The loop returns to its original position when the phosphate departs. This switching movement is transmitted across both types of motor — far from where the fuel triggers the process — by a long helix which moves like a piston.

Overall, the motors have a convoluted mechanism that looks like something dreamt up by Heath Robinson, commented Prof Vale. When the ''feet'' of myosin, which act as enzymes, catalyse the reaction of ATP, the piston drives the movement of a myosin foot from one site on an actin fibre to the next. In a muscle, many moving feet act like levers to drive the fibres past one another, and it contracts.

Kinesins have a pair of feet at one end and a tail at the other, where cargo is carried. The feet lock on to sites along the microtubules and, when driven by ATP-fuelled piston strokes, march the load from one position to another.

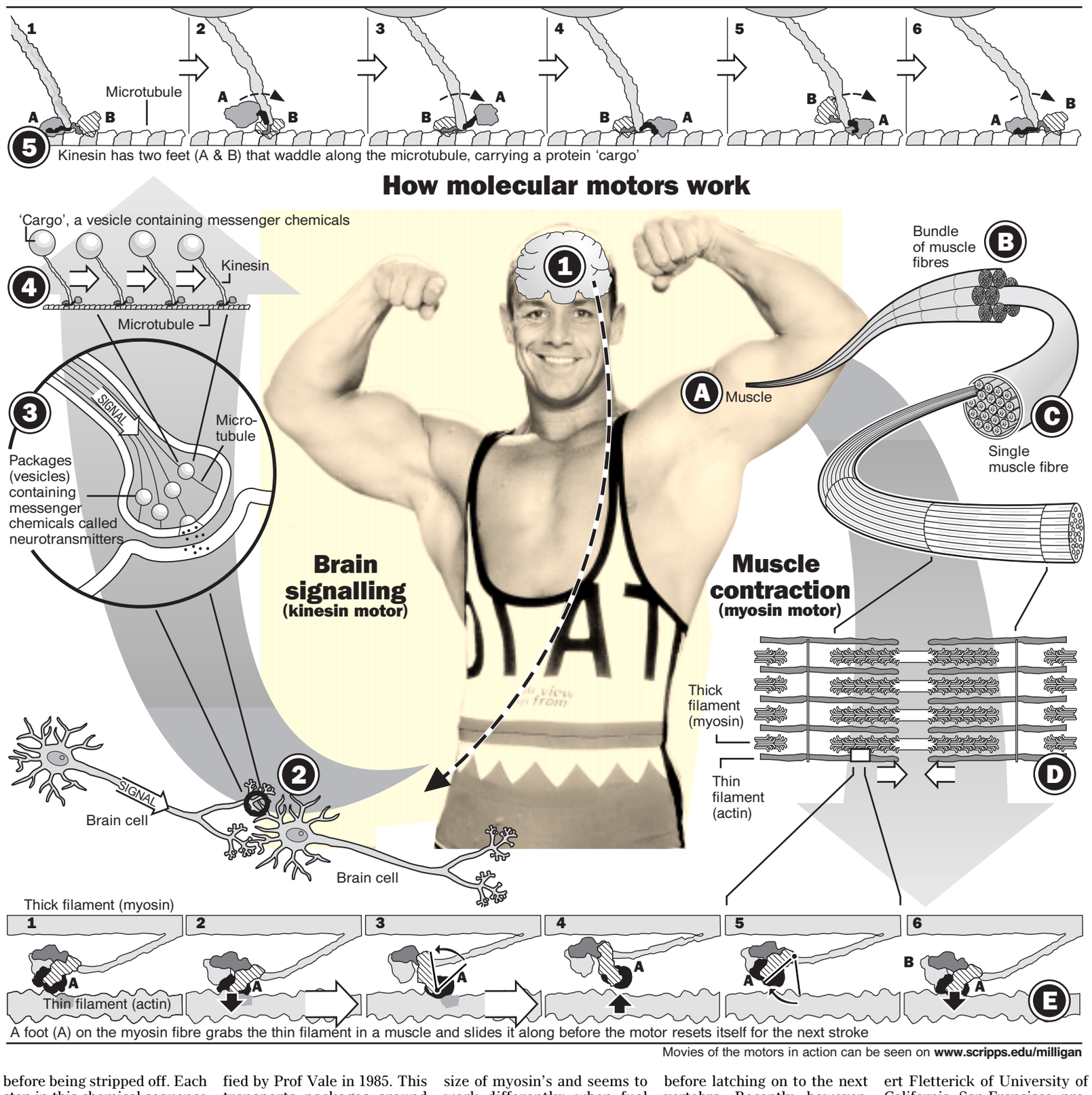
Intriguingly, the same core — switching loops and helix — can be found in another protein family, called G proteins, which act like switches, turning processes on and off in cells. This suggests they all share a common ancestor that evolved more than a billion years ago.

**'Each one of your cells can be thought of as a metropolis'**

No wonder that molecular motors are so widespread. They appear in plants and fungi, indeed any advanced cell (technically, these are cells that have DNA confined within the nucleus).

The real differences between myosin and kinesin lie in the parts of the motors that stick to the actin and microtubule tracks. The feet of myosin are almost twice the size of the dainty pins of kinesin (dynein has clodhoppers that are 10 times bigger). And the ''legs'' are also quite different, though they do move in a similar way.

By studying these motors, scientists hope to uncover the mechanisms of molecular movement, understanding that could help treat disease and design microscopic machines. Learning from nature, ''nanotechnologists'' are even now harnessing purely random molecular movements to shift tiny loads. Given the wonders routinely performed by the machinery in a living cell, man-made molecular engines could prove revolutionary.




Movies of the motors in action can be seen on **www.scripps.edu/milligan**



# Well away with the green fairies

**AS I WALK home from work, I pass through Camden Town. On a warm spring evening the journey is a potent reminder of the joys and miseries of alcohol, from sippers of chardonnay to swiggers of cider. A dingy Georgian house on the way has a marble plaque saying that Verlaine and Rimbaud stayed there in 1873. Each was a member of that great French society of addicts of *l'élixir de la fée verte* (green fairy liquid, in unromantic translation); of absinthe.**

**Absinthe contains an extract of wormwood, a shrub containing a poison found also in sage and certain cypress trees. Its effects were considered so noxious that it was banned by the French government in 1915 in the interests of the war effort. Now comes news of how this magic narcotic works.**

**Chemically, thujone (as the active ingredient is known) is a set of rings of 10 carbon atoms with a shape like that of tetra-hydro cannabinol, the active ingredient of cannabis. To drink too much of it (and today wormwood is sold off the net as a herbal tonic for anxiety) leads to hallucinations, convulsions, and paralysis. To the surrealists (and to the other Frenchmen who sank 36 million litres of absinthe in 1910) it gave a double intoxication, alcohol plus something more. No wonder the state put a stop to it.**

**Because wormwood is a painkiller that also kills flies, malaria parasites and intestinal worms, troops were once dosed with the "green fairy". It was brought to France from Switzerland in 1797 by one Henry Pernod; and its rituals (mainly to hide the bitter taste — see the Greek *apsinthion*, undrinkable), involve filling a spoon with sugar, dripping on the absinthe, setting fire to it and then diluting the burning liquor with water to give a cloudy liquid. Today's Pernod looks much the same. Thujone attaches itself to receptors of a neuro-transmitter called gamma-amino-butyric acid. The chemical is a gate-keeper in the brain. It controls the release of a range of other transmitters that pass messages between nerve cells. Its various receptors are the targets of many psycho-active drugs (such as alcohol itself) and may also be involved in epilepsy, schizophrenia, Alzheimer's disease and, perhaps, addictive and thrill-seeking behaviour in general. Anti-depressants such as valium attach themselves to GABA receptors, as do other chemicals such as the "loco weed" that now and again kills cattle, and insecticides such as dieldrin. Now, absinthe has joined the list.**

**Insects resistant to dieldrin survive a solid dose of thujone, and radioactive labelling shows the thujone molecules making straight for the receptors. They avoid, though, the docking sites for tetra-hydro-cannabinol so that absinthe's hallucinatory effects are not related to cannabis; instead, thujone excites and alerts the brain.**

**Prof Steve Jones**
View from the lab

**That, then, is why Alfred Jarry careered around Paris on a bicycle with his face painted green, and why Van Gogh cut off his ear. Degas's famous *Absinthe Drinker*, depressed though she looks (and of whom it was said that "Absinthe makes the tart grow fonder") had a set of buzzing nerve cells in her head. Oscar Wilde, too, was right when he said: "After the first glass you see things as you wish they were. After the second you see things as they are not. Finally, you see things as they really are; and that is the most horrible thing in the whole world."**

**One scientist has tried to work out what absinthe might really have done to its adepts. He calculates that the amount of thujone per glass is so small that any drinker would fall off his chair well before the hallucinations set in. To suffer from thujone toxicity he would have to drink 50 green fairies in a row — which, as the potion is twice as strong as whisky, might have interesting side-effects.**

**However, cheap absinthe contained other chemicals. Analysis shows traces of methyl alcohol, copper salts, aniline green for its colour, and antimony chloride to make it cloudier when water was added.**

**All those, no doubt, were harmful; but the sad fact remains that the big killer in absinthe is also found in chardonnay and cider. The great decadents would have felt at home in today's Camden: Verlaine died of drink at 52, Rimbaud at 37.**