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How giant viruses could rewrite the story of life on Earth

They're huge and they lurk everywhere. But don't fear, these giants seem to be gentle – and might even have taught our own cells a few neat tricks

THEY found the mystery microbe in a water tower in Bradford in 1992. This city in northern England is not, perhaps, the first place you'd expect to find exotic life forms. But whatever it was looked bizarre under a microscope. It was a hairy, 20-sided polyhedron, which hinted that it was a virus. But it seemed far too big for that. And closer inspection revealed a complexity totally out of line with what biologists thought possible for these infectious agents that inhabit the shadowy borders of life.

Yet virus it was. And since "mimivirus" was eventually confirmed as such in 2003, discoveries of surprisingly enormous viruses have kept coming. Not only do giant viruses seem to be all over the place, but their world is more vast and diverse than we us who we are. “If we want to understand evolution and the origins of life, viruses have to be taken into account,” says Patrick Forterre, a molecular biologist at the Pasteur Institute in Paris, France.

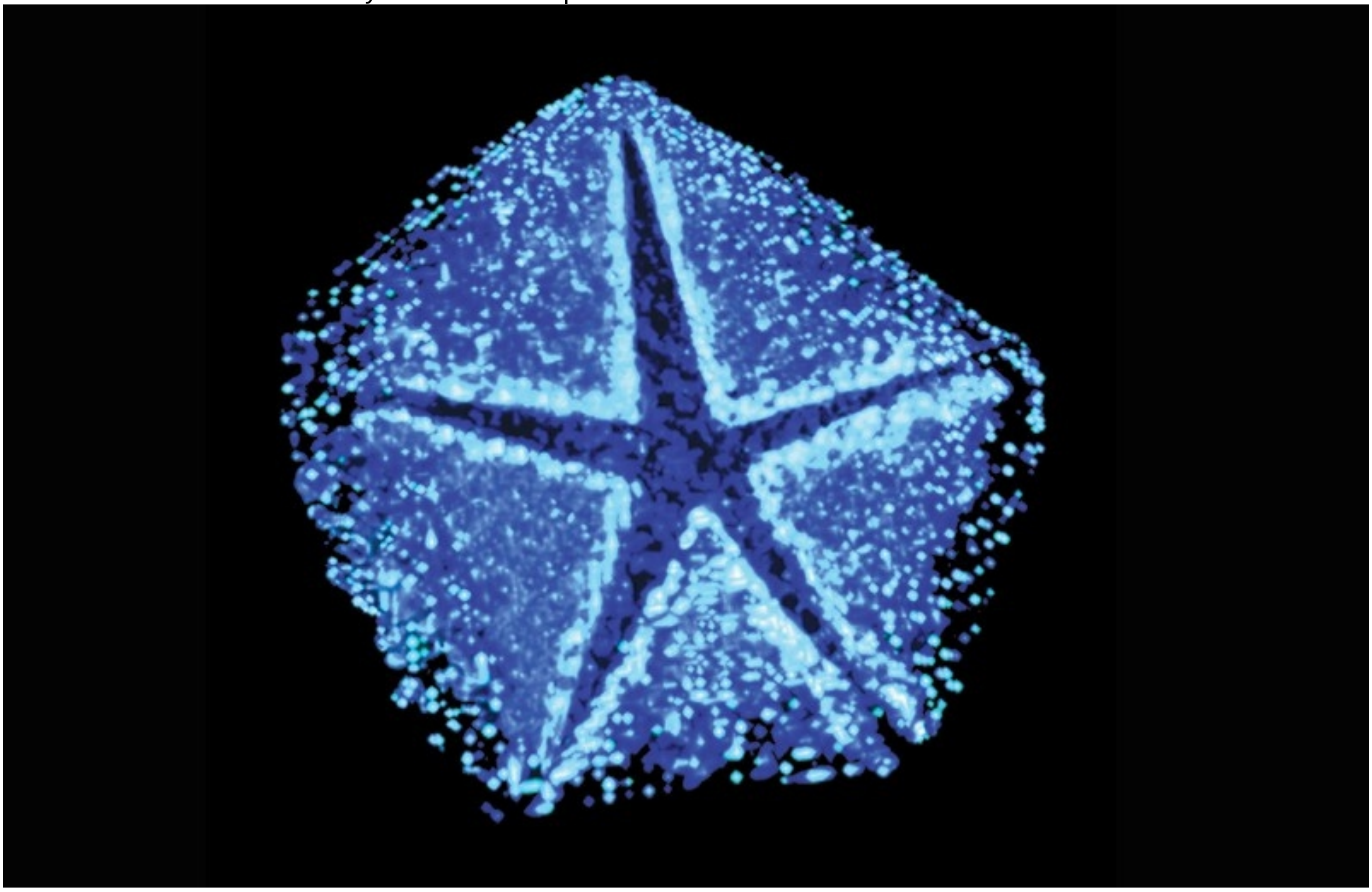
Biologists have been loath to allow viruses the prestige of being labelled as alive because they can do little without a host. They are parasites, injecting their genetic instructions into a cell and hijacking its biochemical machinery to produce the parts for spawn. Many of them do little more than replicate, which means they don’t need many genes. Human immunodeficiency virus (HIV), for instance, has just nine. It turns out that mimivirus, in contrast, has 1018.

The other piece of received wisdom about viruses is that they are small. This assumption dates back to 1892, when they were discovered by Dmitri Ivanovsky, a Russian botanist puzzling over an unknown disease ravaging tobacco crops. He filtered the sap from diseased plants through porcelain and found that it remained infectious. Since the pores in the filters were smaller than any bacterium, the conclusion was that the sickness must have been caused by something much tinier. They were later named viruses.

It was partly because of these preconceptions that giant viruses escaped detection for so long. Mimivirus was collected from that Bradford water tower when researchers were looking for the source of a pneumonia outbreak at a nearby hospital. But it was dismissed as just another unclassifiable bacterium, stuck in a freezer and forgotten.

In 1998, a French scientist named Bernard La Scola took another look. He became intrigued because the microbe didn’t have any ribosomes, the factories that make proteins and are a hallmark of all cellular life. But the clinching evidence came when a group of scientists showed that the entity didn’t divide its cells to reproduce, as all bacteria do. This was definitely a virus.

Over the next decade, Abraham Minsky of the Weizmann Institute of Science in Rehovot, Israel, started delving further into what makes mimivirus tick. Among his first discoveries was a peculiar five-armed star shape that looked almost like it had been tattooed on the virus (see image). “We saw this amazing fivefold structure,” Minsky says, “and we had no idea whatsoever what it was.”



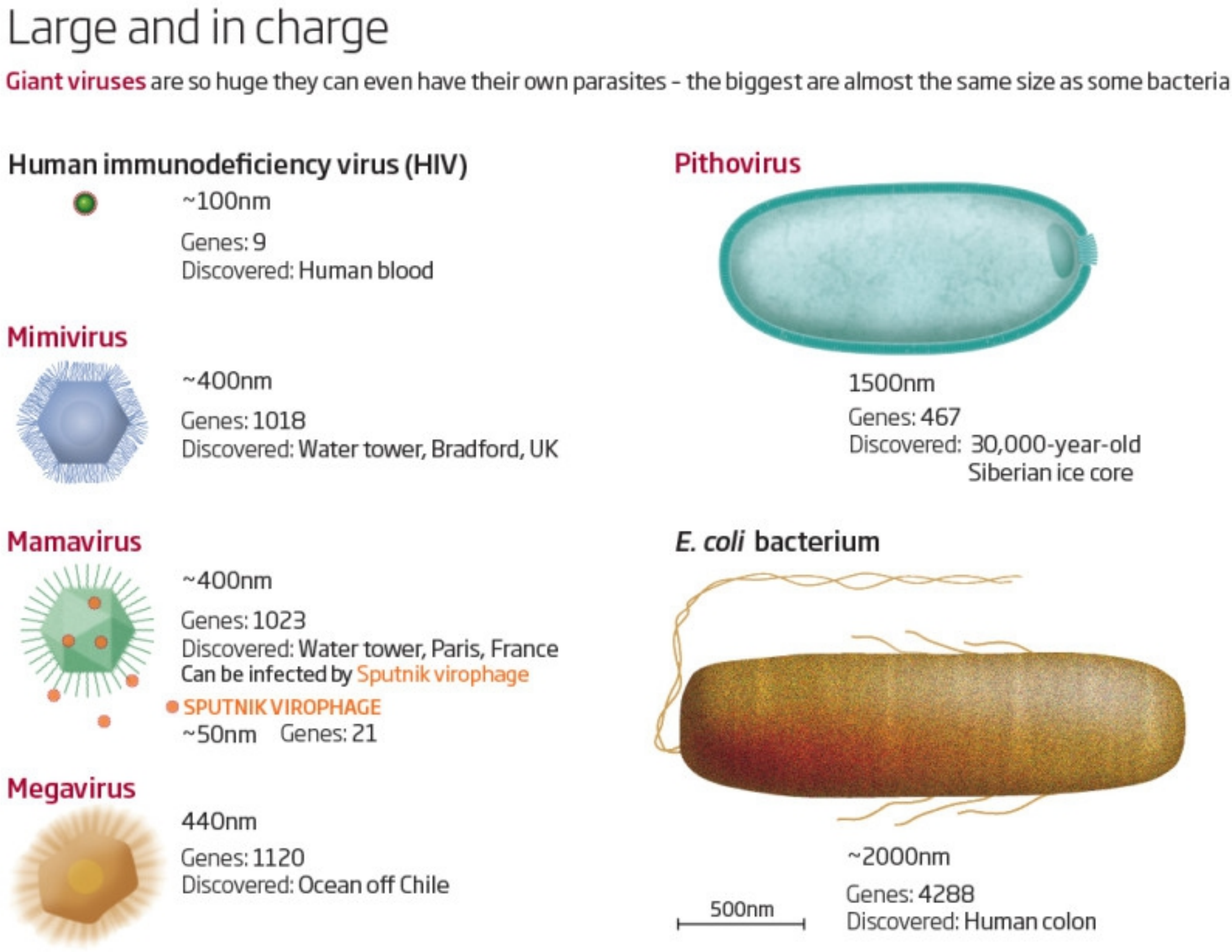
It turned out to be the seam of a portal consisting of five triangular panels that swing outwards during infection, allowing the contents of the viral particle to be released into the host. Nobody had seen anything like it before. Minsky named it the “stargate”.

Minsky also looked at the virus factory that mimivirus creates. Several conventional viruses were already known to set up such an assemblage, which acts like a workshop inside the host cell that churns out virus progeny. None, however, are quite like this one. The mimivirus staffs its factory with the cell’s own ribosomes, which make proteins, and mitochondria, which provide power. It’s also huge compared with other known factories, big enough to hold hundreds of new viruses. “We still do not know what the mechanism is by which the ribosomes, mitochondria and so on are recruited,” says Minsky. “But clearly it’s a very efficient, very directed process.”

Finding out how giant viruses work now feels like a more urgent quest, especially since we’ve discovered that they are just about everywhere.

One of those who has helped confirm this is Jean-Michel Claverie, a virologist at Aix-Marseille University in France, who was part of the team that first identified mimivirus in 2003. “I suspect there are more very large viruses that have escaped detection,” he said at the time. “When you think about it, there really is no limit for how big a virus can be.” Since then, he and his wife Chantal Abergel have been on a mission to find more specimens.

The first discovery, however, went to another researcher at the same university, Didier Raoult. He began searching in the most obvious place: more water towers. And sure enough, he struck gold in Paris, discovering a specimen he named mamavirus. But the big news was what they found inside it: the Sputnik virophag. It was the first ever sighting of a virus that infects another virus. (Sputnik translates from Russian as “fellow traveller”.) The discovery provided fuel for the argument that viruses are somehow alive, since evidently mamavirus can get “sick”.



Then in 2010, Raoult published the results of a wider search showing that new strains – 19 in total – cropped up in other water samples taken from rivers, lakes, fountains and taps.

Things mushroomed from there. The following year, Claverie found an even bigger virus – he named it megavirus – in the ocean off Chile. And in mud samples taken from a river in Chile and a pond in Australia, he and his team unearthed two examples of what is now known as pandoravirus. One had about 1500 genes – the other had more than 2550.

Then came perhaps the most impressive specimen. In ice core samples that froze 30,000 years ago, Claverie found the spectacular pithovirus. At roughly 1.5 micrometres long, this beast is as big as some common bacteria (see "Large and in charge"). It also has weird features including a hole in its membrane that is capped by a "cork".FIG-mg30570801.jpg

"Now we realise giant viruses are basically everywhere," says Claverie. "I'm sure if we looked with the right methods, we would find them in your garden." They also turn up inside us (see "Big unfriendly giants?").

The question now bothering biologists is: where did these things come from, and where do they fit into the established classification system for life?

At its coarsest level, this system consists of eukaryotes, bacteria and archaea. Eukaryotes are cells like those that make up animals and plants, with their DNA neatly divisions were thought to encompass all living organisms.

The strange thing about giant viruses is that when you take a peek at their genes, they don't seem to fit in anywhere. For any given giant virus, between 50 and 90 per cent of their genes are not known anywhere else. Even the different families of giant virus do not share many. How can this be?

Claverie has a radical suggestion: that giant viruses are the remnants of long extinct domains of life that were completely different from the cells that exist today. It is domains, plural, he says, because the giant viruses are all so different.

Beyond bounds

"With the mimivirus we argued that we need to invent a fourth domain of life," he says. "Now we believe it is no longer just a fourth domain, but a fifth, a sixth and a seventh."

His idea is not without support. In 2012, a team led by Gustavo Caetano-Anollés of the University of Illinois at Urbana-Champaign created an evolutionary tree based on grouping viruses and cells that have similar protein structures. This makes giant viruses seem to be more ancient than anything else, supporting Claverie's theory that they come from extinct lineages.

On the other hand, many argue that the supposedly unique genes aren't what they seem. They think that viruses evolve much faster than cells, so if you see a gene you don't recognise, it's more likely to be a familiar one mutated beyond recognition than evidence of an unknown domain of life.

"There is absolutely no indication that the giant viruses originated from an extinct or unknown domain of cellular life," says Eugene Koonin, an evolutionary geneticist at the National Center for Biotechnology Information in Bethesda, Maryland.

Yet Claverie remains resolute. The idea that viruses evolve more quickly than cells doesn't necessarily apply to viruses that use DNA rather than RNA, as the giant viruses do, he claims. And his own studies show that giant virus genes don't evolve faster than host genes. He also argues that all genomes should get smaller, not larger, once they adopt a parasitic lifestyle, because they make use of the host's resources. That means giant viruses must be older than the small viruses we're familiar with, he reckons.

Whatever the truth, viruses clearly have their own way of doing things. "They are certainly playing around with evolution more than anything else on the planet," says Curtis Suttle, a marine virologist at the University of British Columbia in Vancouver, Canada.

One example is the discovery that mimivirus has its own way of making collagen, a protein that crops up in everything from skin to tendons and makes up roughly a quarter of the weight of proteins in most mammals.

But if they are engines for genetic novelty, viruses are also generous with their creations, spreading genes and influencing the evolution of their hosts. So far, we have mostly found giant viruses that infect amoebas. But in 2014, Jonathan Filée, an evolutionary geneticist at Paris-Sud University in France, showed that 23 core giant virus genes can be found in a selection of cellular organisms, including a moss and a gelatinous freshwater animal known as a hydra. It was an indirect pointer that giant viruses infect them too.

“For a long time, we thought viruses were stealing genes from the host,” says Claverie. “Now it’s becoming clearer that viruses often transmit genes to their hosts.”

This process might have had serious impacts on the evolution of cells that went on to become life like us. Take the nucleus inside all our cells, for instance. For decades, scientists have kicked around the idea that this was a virus that never left. The idea is largely based on speculation, yet giant viruses might finally provide some backing for it.

In 2013, a team in the US showed that the mimivirus factory is built from the same stuff as the nucleus of the infected amoeba. They also happen to be the same size. It’s far from solid proof, but some see this as a hint of an evolutionary link.

“Large DNA viruses probably played an important role in the emergence of eukaryotes by bringing many new genes,” says Forterre. It is possible, he thinks, that the ancestors of modern eukaryotic cells learned how to manipulate membranes and make a nucleus from viruses.

This tangled fallout from the discovery of giant viruses is also changing the way that Forterre, Claverie and others think of life. They say that a virus should not be defined by its inert particle phase, but by the form it takes when united with the genome of its host. In this state, they argue, a virus resembles a parasitic bacterium and is alive. Of course, this living organism isn’t anything like the ones we’re used to, which is why they also say we need to broaden our thinking. Defining life only as autonomous, ribosome-bearing cells “is totally too rigid”, says Claverie. And Raoult has proposed a division of life into ribosome-bearing “ribocells” and virus-driven “virocells”.

Semantics aside, it’s clearer than ever that the boundary between life and viruses is a blurry one. “It’s no longer possible to say that viruses are not living and cells are living,” says Forterre.

What comes next is anyone’s guess. The search for giant viruses has so far centred largely on amoebas, partly because they are a known host that is straightforward to grow and study in labs. That means there are multitudes of potential hosts still to sift through. For Claverie, that’s a daunting and exciting prospect: “We don’t know what a virus is any more – or what to expect next.”

(Images: Artwork: Arthur Chiverton; Abraham Minsky/ The Weizmann Institute of Science)

Big unfriendly giants?

Giant viruses are probably all around us (see main story). There's also evidence that they hang out inside our bodies: they have been found in human blood and even a contact lens case. Plus, several studies have linked them with diseases like pneumonia. So are they a threat to us?

So far, no major alarms have been sounded. But researchers have shown that one giant virus can get into a type of white blood cell called a macrophage. A study of people with pneumonia also showed that a small fraction had antibodies against the virus in their blood. This has led some to suggest that giant viruses play some role in human diseases. We don't yet know if that's true or what the role might be.

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