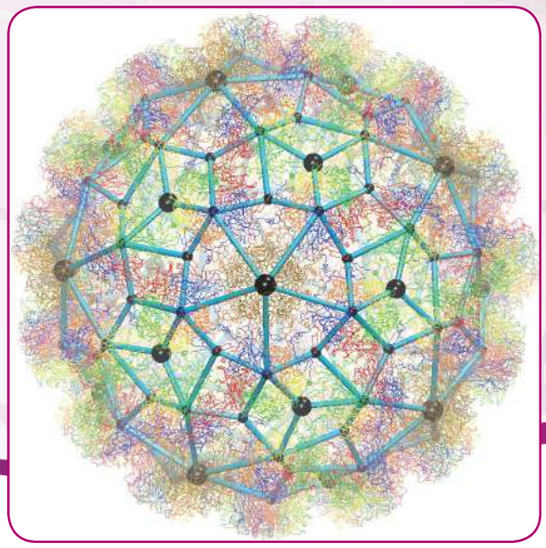
MATHEMATICS MATTERS

Fighting Infections with Symmetry



Many viruses have a symmetrical structure made from basic building blocks, and biologists have struggled to explain some of the more detailed shapes. Now, mathematicians are using complex theories of symmetry to reveal these viral structures, ultimately leading to new treatments for diseases.

Viruses are responsible for a variety of illnesses, ranging from the common cold to more serious conditions such as AIDS and some types of cancer, but their methods of infection are always similar. Once a virus has entered a host's body, it hijacks the replicating mechanisms within the host's cells and starts pumping out copies of itself. Viruses can only do this by concealing their genomic material within a protein shell, or capsid, which allows them to slip inside the host's body like a Trojan horse. These capsid shells often have complex symmetrical structures, so mathematicians are investigating their shapes in the hope of discovering new treatments for viral infections.

A virus is essentially just a short string of DNA (or RNA, a related molecule) wrapped inside a capsid shell, and longer strings of genomic material require a larger shell to hold them. This creates a problem because the genomic material must describe the entire virus, including the capsid, and a larger shell in turn requires a longer string of DNA or RNA.

Francis Crick and James Watson, the biologists who also discovered the structure of DNA, suggested in 1956 that symmetrical capsids provide a solution as they can be constructed from just a few basic building blocks. This means the genomic material of a symmetrical virus can be much smaller, because it simply needs to describe small sections of the capsid and instructions for repeating them in a symmetrical pattern.

It was later found that many viruses use icosahedral symmetry to compact their genome, as their capsids resemble a shape made from 20 triangular faces called an icosahedron. It can be rotated in 60 different ways and still appear to be the same – in other words, it has 60 axes of symmetry.

> "Modelling the structure of viruses could have enormous ramifications for drug design and the development of new treatments."

Although this model works well for small viruses with 60 proteins, it cannot explain the structures of larger capsids, suggesting there is a more intricate pattern at work. The biologists Donald Caspar and Aaron Klug discovered this pattern in 1962, when they realised that dividing the 20 triangles of an icosahedron into smaller triangles could explain more complicated viruses than Crick and Watson's simple icosahedron model.

The Caspar-Klug model is now the standard way of explaining capsid structures, but there are still some viruses that don't quite fit. Human papilloma viruses, the major cause of cervical cancer and a factor in other cancers, have a five-fold or pentagonal structure that doesn't match with traditional ideas of symmetry, because a pentagon cannot be built from regular triangles. Crick and Watson's theory that viruses are constructed from a few symmetrically-arranged building blocks seemingly doesn't work for papilloma viruses, but Reidun Twarock at the University of York has found a fix based on decades-old pure mathematics.

In the 1970s, the English mathematical physicist Roger Penrose discovered a way of combining two four-sided shapes called the "kite" and "dart" to produce patterns with five-fold symmetry. Unlike regular pentagons, these two shapes fit together without leaving any gaps. They also differ from squares or triangles, because the patterns they produce don't ever repeat themselves. It turns out that by using Penrose's concept in three dimensions, Twarock was finally able to model the capsid structure of complicated viruses like human papilloma.

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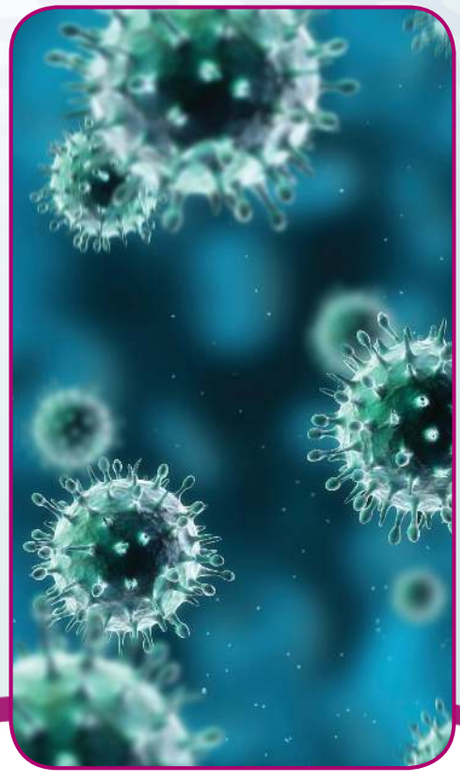
Twarock's work even allows her to peer inside the capsid shell and understand how it connects to the virus's genomic material. The Caspar-Klug model can only explain the capsid's surface, so biologists currently rely on complicated imaging techniques such as cryo-electron microscopy to understand the structure of the entire virus. Now, Twarock has been able to accurately predict characteristic features of a virus's internal structure, and has found links between the external shape of the protein container and the organisation of the viral genome inside.

Modelling virus structures in this way could have enormous ramifications for drug design and the development of new treatments. Biologists know that some viruses change their shape when infecting a host cell, rearranging their capsid shells in order to release their genomic material, but exactly how this transition occurs is unclear. By classifying the possible shapes that a virus can take, Twarock hopes to model the various stages a virus goes through as it changes and work out which shapes are most likely to occur. This will ultimately help develop methods that inhibit these structural changes and prevent viral infection.
Her mathematical research could also help turn the tables on viruses, hijacking their capsid shells for use in drug delivery. Researchers working in this area currently select viruses based on the host cells that they target, then replace the viral genomic material with an alternative, beneficial sequence. Twarock's insight could help them choose viruses based on the properties of a particular capsid shape, allowing for better-targeted treatments.

In addition to the medical benefits, Twarock could also help settle a biological argument about the origin of viruses. Many viruses share similar shapes despite having very different genetic sequences, a puzzle that biologists have yet to solve. Some suggest these similar viruses must have evolved from a distant common ancestor, but others argue that genetic differences make this impossible. Twarock's work indicates that these shapes could result from mathematical limitations, and that different viruses have similar structures because there are only so many that are actually possible.

A typical virus is 10,000 times smaller than a grain of sand, but their structures are so intricate that the simple biological models developed by Crick and Watson and then Caspar and Klug were not able to fully capture the details. It has taken Twarock's advanced pure mathematics to make sense of them, allowing biologists to study viruses in greater detail than ever before. The more we understand about virus shapes, the better equipped we are to fight their infections, so studying their symmetry will ultimately help save lives.



TECHNICAL SUPPLEMENT

Icosahedral symmetry

The icosahedron is one of the five Platonic solids, the only shapes that can be constructed from identical polygonal faces, and its many symmetries have been well studied by mathematicians. It is said to have 5:3:2 symmetry, as there are six 5-fold axes of symmetry, ten 3-fold axes of symmetry and fifteen 2-fold axes of symmetry. This structure allowed Crick and Watson to identify the placement of various proteins on a virus's capsid shell for some small viruses.

Their model predicts that any protein not sitting on an axes of symmetry must appear in multiples of 60, but symmetry cannot account for the placement of more than 60 proteins, and further conditions are needed to pinpoint exactly where all proteins are located. Caspar and Klug partially solved this problem by overlaying an additional triangular lattice on to the icosahedral model, and Twarock takes this further with a quasilattice derived from Penrose tiles.

Penrose tiles

There are only three regular polygons that tile the plane: squares, triangles, and hexagons. These three shapes fit together in regular grids that exhibit rotational, reflectional and translational symmetry, but they are not the only tilings possible. Roger Penrose's irregular kite and dart shapes also tile the plane, displaying both reflectional and 5-fold rotational symmetry, but not translational symmetry. In other words, Penrose tilings are aperiodic and never repeat themselves.

Penrose was not the originator of aperiodic tiling, but he was the first to show it could be done with just two shapes. Although Penrose tiles were originally the result of mathematical curiosity, they found an application in the mid 1980s with the discovery of quasicrystals, an unusual atomic structure found in some metallic alloys that could only be explained by Penrose's work. Now, Twarock's research shows that Penrose tilings can also be applied to the structure of viruses.

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