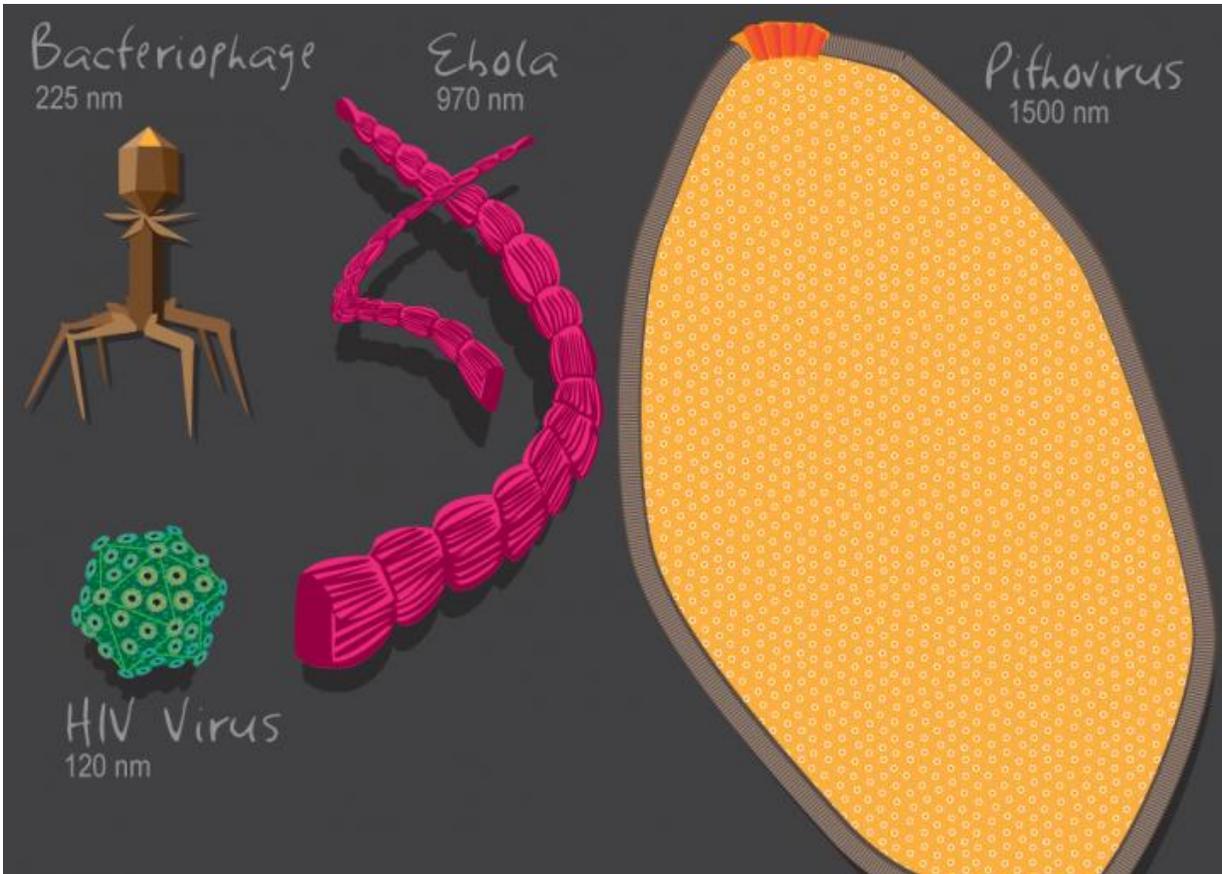


Study adds to evidence that viruses are alive

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The diverse physical attributes, genome sizes and lifestyles of viruses make them difficult to classify. A new study uses protein folds as evidence that viruses are living entities that belong on their own branch of the tree of life. Credit: Julie McMahon

A new analysis supports the hypothesis that viruses are living entities that

share a long evolutionary history with cells, researchers report. The study offers the first reliable method for tracing viral evolution back to a time when neither viruses nor cells existed in the forms recognized today, the researchers say.

The new findings appear in the journal *Science Advances*.

Until now, [viruses](#) have been difficult to classify, said University of Illinois crop sciences and Carl R. Woese Institute for Genomic Biology professor Gustavo Caetano-Anollés, who led the new analysis with graduate student Arshan Nasir. In its latest report, the International Committee on the Taxonomy of Viruses recognized seven orders of viruses, based on their shapes and sizes, genetic structure and means of reproducing.

"Under this classification, viral families belonging to the same order have likely diverged from a common ancestral virus," the authors wrote. "However, only 26 (of 104) viral families have been assigned to an order, and the evolutionary relationships of most of them remain unclear."

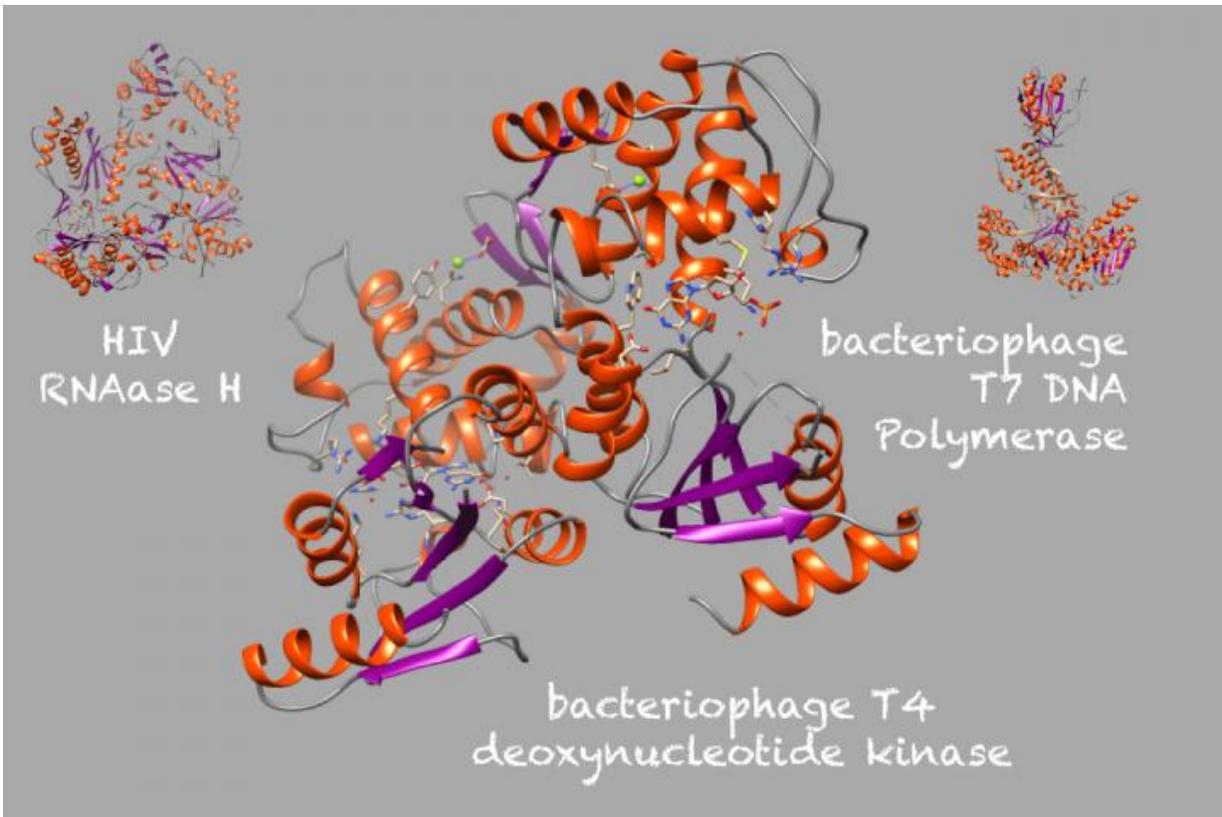
Part of the confusion stems from the abundance and diversity of viruses. [Less than 4,900](#) viruses have been identified and sequenced so far, even though scientists estimate there are more than a million viral species. Many viruses are tiny - significantly smaller than bacteria or other microbes - and contain only a handful of genes. Others, like the recently discovered mimiviruses, are huge, with genomes bigger than those of some bacteria.

The new study focused on the vast repertoire of protein structures, called "folds," that are encoded in the genomes of all [cells](#) and viruses. Folds are the structural building blocks of proteins, giving them their complex, three-dimensional shapes. By comparing fold structures across different

branches of the tree of life, researchers can reconstruct the evolutionary histories of the folds and of the organisms whose genomes code for them.

The researchers chose to analyze protein folds because the sequences that encode viral genomes are subject to rapid change; their high mutation rates can obscure deep evolutionary signals, Caetano-Anollés said. Protein folds are better markers of ancient events because their three-dimensional structures can be maintained even as the sequences that code for them begin to change.

Today, many viruses - including those that cause disease - take over the protein-building machinery of host cells to make copies of themselves that can then spread to other cells. Viruses often insert their own [genetic material](#) into the DNA of their hosts. In fact, the remnants of ancient viral infiltrations are now permanent features of the genomes of most cellular organisms, including humans. This knack for moving genetic material around may be evidence of viruses' primary role as "spreaders of diversity," Caetano-Anollés said.



A new study analyzes the distinct, three-dimensional structures found in proteins. These structures are called folds. Some folds are shared by all organisms, while others are unique to individual branches of the tree of life. Pictured here are folds found in viruses. Credit: Arshan Nasir

The researchers analyzed all of the known folds in 5,080 organisms representing every branch of the tree of life, including 3,460 viruses. Using advanced bioinformatics methods, they identified 442 protein folds that are shared between cells and viruses, and 66 that are unique to viruses.

"This tells you that you can build a tree of life, because you've found a multitude of features in viruses that have all the properties that cells have," Caetano-Anollés said. "Viruses also have unique components

besides the components that are shared with cells."

In fact, the analysis revealed genetic sequences in viruses that are unlike anything seen in cells, Caetano-Anollés said. This contradicts one hypothesis that viruses captured all of their genetic material from cells. This and other findings also support the idea that viruses are "creators of novelty," he said.

Using the protein-fold data available in online databases, Nasir and Caetano-Anollés used computational methods to build trees of life that included viruses.

The data suggest "that viruses originated from multiple ancient cells ... and co-existed with the ancestors of modern cells," the researchers wrote. These ancient cells likely contained segmented RNA genomes, Caetano-Anollés said.

The data also suggest that at some point in their evolutionary history, not long after modern cellular life emerged, most viruses gained the ability to encapsulate themselves in protein coats that protected their genetic payloads, enabling them to spend part of their lifecycle outside of host cells and spread, Caetano-Anollés said. The protein folds that are unique to viruses include those that form these viral "capsids."

"These capsids became more and more sophisticated with time, allowing viruses to become infectious to cells that had previously resisted them," Nasir said. "This is the hallmark of parasitism."

Some scientists have argued that viruses are nonliving entities, bits of DNA and RNA shed by cellular life. They point to the fact that viruses are not able to replicate (reproduce) outside of host cells, and rely on cells' protein-building machinery to function. But much evidence supports the idea that viruses are not that different from other living

entities, Caetano-Anollés said.

"Many organisms require other organisms to live, including bacteria that live inside cells, and fungi that engage in obligate parasitic relationships - they rely on their hosts to complete their lifecycle," he said. "And this is what viruses do."

The discovery of the giant mimiviruses in the early 2000s challenged traditional ideas about the nature of viruses, Caetano-Anollés said.

"These [giant viruses](#) were not the tiny Ebola virus, which has only seven genes. These are massive in size and massive in genomic repertoire," he said. "Some are as big physically and with genomes that are as big or bigger than bacteria that are parasitic."

Some giant viruses also have genes for proteins that are essential to translation, the process by which cells read gene sequences to build proteins, Caetano-Anollés said. The lack of translational machinery in viruses was once cited as a justification for classifying them as nonliving, he said.

"This is no more," Caetano-Anollés said. "Viruses now merit a place in the tree of life. Obviously, there is much more to viruses than we once thought."

More information: Paper: A phylogenomic data-driven exploration of viral origins and evolution, *Science Advances*, 2015. DOI: [10.1126/sciadv.1500527](https://doi.org/10.1126/sciadv.1500527) , advances.sciencemag.org/content/1/8/e1500527

Provided by University of Illinois at Urbana-Champaign

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