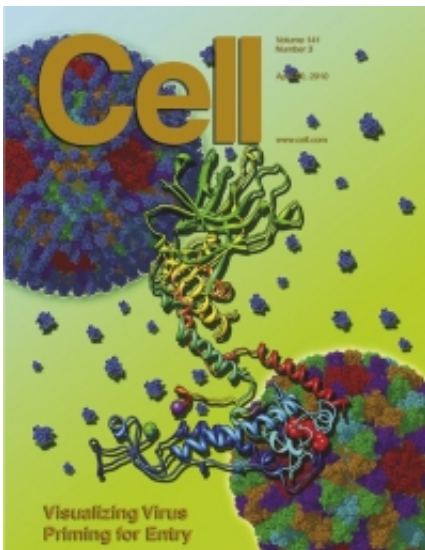


Cryo-electron microscope 'sees' atoms for first time

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Artistic representation of a Cryo-EM 3-D reconstruction of aquareovirus

(PhysOrg.com) -- UCLA researchers report in the April 30 edition of the journal *Cell* that they have imaged a virus structure at a resolution high enough to effectively "see" atoms, the first published instance of imaging biological complexes at such a resolution.

The research team, led by Hong Zhou, UCLA professor of microbiology, immunology and [molecular genetics](#), used cryo-electron microscopy to image the structure at 3.3 angstroms. An angstrom is the smallest recognized division of a chemical element and is about the

distance between the two [hydrogen atoms](#) in a water molecule.

The study, the researchers say, demonstrates the great potential of cryo-electron microscopy, or Cryo-EM, for producing extremely high-resolution images of biological samples in their native environment.

"This is the first study to determine an atomic resolution structure through Cryo-EM alone," said Xing Zhang, a postdoctoral candidate in Zhou's group and lead author of the *Cell* paper. "By proving the effectiveness of this [microscopy technique](#), we have opened the door to a wide variety of biological studies."

With traditional light microscopy, a magnified image of a sample is viewed through a lens. Some samples, however, are too small to diffract visible light (in the 500 to 800 nm range, or 5,000 to 8,000 angstroms) and therefore cannot be seen. To image objects at the sub-500 nm scale, scientists must turn to other tools, such as atomic force microscopes, which use an atomically thin tip to generate an image by probing a surface, in much the same way a blind person reads by touching Braille lettering.

With [electron microscopy](#), another sub-500 nm technology, a beam of electrons is fired at a sample, passing through empty areas and bouncing off dense areas. A digital camera reads the path of the electrons passing through the sample to create a two-dimensional projection image of the sample. By repeating this process at hundreds of different angles, a computer can construct a three-dimensional image of the sample at a very high resolution.

Zhou is faculty director of the Electron Imaging Center for Nanomachines (EICN) at UCLA's California NanoSystems Institute, which is using cryo-electron microscopy to create 3-D reconstructions of nano-machineries, nano-devices and biological nano-structures, such as

viruses.

Structurally accurate 3-D reconstructions of biological complexes are possible with cryo-electron microscopy because the samples are flash frozen, which allows them to be imaged in their native environment, and the microscope operates in a vacuum, because electrons travel better in that environment. The *Cell* paper focused on a structural study of the aquareovirus, a non-envelope virus that causes disease in fish and shellfish, in an effort to better understand how non-envelope viruses infect host cells.

"We are extremely excited about the recent breakthrough achieved by Hong Zhou and his team at the EICN lab," said Leonard H. Rome, senior associate dean for research at the David Geffen School of Medicine at UCLA and associate director of the California NanoSystems Institute. "The ability to understand the structure of viruses at an atomic level will open avenues for manipulating them for use in drug delivery and propel numerous innovations in treatments of diseases. UCLA is fortunate to have such specialized instrumentation and the expertise of Professor Zhou and his team to take advantage of these marvelous microscopes."

Viruses can be classed into two types: envelope and non-envelope. Envelope viruses, which include influenza and HIV, are surrounded by an envelope-like membrane which the virus uses to fuse with and infect a host cell. Non-envelope viruses lack this membrane and instead use a protein to fuse with and infect cells. This process was poorly understood until Zhou's study.

"Through better knowledge of virus structures, we hope to engineer medications in three ways," Zhou said. "If we understand how viruses work, first we can identify small molecules or drugs that block their infection; second, we can engineer ultra-stable and non-infectious virus-like particles as optimal vaccines; and third, we can alter their

characteristics so that instead of delivering a disease, viruses could deliver medications.

"Indeed, we are working with UCLA physicians and engineers to engineer viruses for gene therapy and drug delivery," he said. "In essence, we hope to take advantage of millions of years of evolution that have made viruses incredibly effective delivery platforms."

From the high-resolution 3-D images produced with the cryo-electron microscopy, Zhou's group was able to determine that the aquareovirus employs a priming stage to accomplish cell infection. In its dormant state, the virus has a protective protein covering, which it sheds during priming. Once the outer shell has been shed, the virus is in a primed state and is ready to use a protein called an "insertion finger" to infect a cell.

The team's study ushers in a new era of structural biology for understanding important biological processes. The group was able to discover this functionality because of the accurate structural model produced through cryo-electron microscopy. In addition to producing a high-resolution 3-D image of samples, the technology allows samples to be imaged in their native environment, so the structural model is faithful to the original sample. From a technical point of view, this work also demonstrates the power of cryo-electron microscopy in obtaining 3-D structures of biological complexes without needing to grow a crystal.

More information: [www.cell.com/abstract/S0092-8674\(10\)00360-0](http://www.cell.com/abstract/S0092-8674(10)00360-0)

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