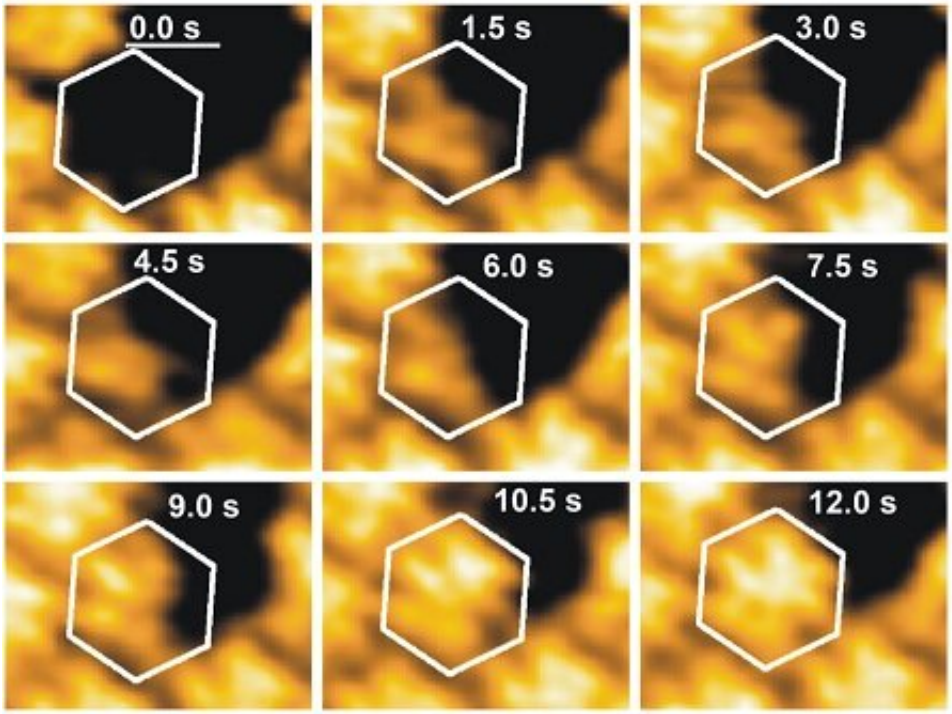
Physical virology shows the dynamics of virus reproduction

January 14 2021



Dynamics of self-assembly of a viral protein structure. The white hexagon marks the position where a hexamer at the edge of the growing lattice gradually forms from the single viral protein subunits. Credit: Wouter Roos

The reproductive cycle of viruses requires self-assembly, maturation of virus particles and, after infection, the release of genetic material into a host cell. New physics-based technologies allow scientists to study the dynamics of this cycle and may eventually lead to new treatments. In his

role as physical virologist, Wouter Roos, a physicist at the University of Groningen, together with two longtime colleagues, has written a review article on these new technologies, which was published in *Nature Reviews Physics* on 12 January.

"Physics has been used for a long time to study viruses," says Roos. "The laws of physics govern important events in their reproductive cycle." Recent advances in physics-based techniques have made it possible to study self-assembly and other steps in the reproductive cycle of single virus particles and at sub-second time resolution. "These new technologies allow us to see the dynamics of viruses," Roos adds.

Energy

In 2010, he first published a review article on the physics aspects of virology with two of his colleagues. "Back then, almost all of the research on viruses was relatively static, for example exerting pressure on a virus particle to see how it responded." At that time, studies on dynamic processes, such as self-assembly, were performed in bulk, without the option to zoom in on individual particles. "This has changed over the last couple of years and therefore, we thought it was time for another review." This paper, "Physics of Viral Dynamics," was co-authored by Robijn Bruinsma from the University of California in Los Angeles (USA) and Gijs Wuite from VU Amsterdam (the Netherlands).

Viruses hijack cells and force them to make the protein building blocks for new virus particles and to copy their genetic material (either RNA or DNA). This results in a cellular soup full of virus parts, which self-assemble to produce particles of encapsulated RNA or DNA. "No external energy is required for this process. And even in vitro, most viruses will self-assemble quickly." This process was traditionally studied in bulk material, averaging out the behavior of large numbers of virus particles. "So, we had no idea of the variance in the assembly of

individual particles."

Sub-second scans

Over the last few years, technologies have been developed to study these individual particles in real-time. One of those is fast Atomic Force Microscopy (AFM). An atomic force microscope scans surfaces with an atom-sized tip and is therefore able to map their topology. "Recently, the scanning speed of AFM increased dramatically and now we can carry out sub-second scans of surfaces that measure less than 1 micrometer squared using High-Speed AFM," says Roos, who uses an AFM himself. "This allows us to see how virus subunits assemble on a surface. It is a very dynamic process, with building blocks attaching and releasing."

Single-molecule fluorescence is also used to study viruses, for example, the attachment of viral proteins to DNA. "Using optical tweezers, we hold two tiny beads on either end of a DNA molecule. When viral proteins bind to the DNA, this will coil up and bring the two beads closer together. This is visualized by fluorescent markers attached to the beads." Alternatively, proteins with fluorescent markers can be observed while they attach to viral DNA or to other proteins. A third technology is to use an optical microscope to measure interference of light that is scattered by virus particles. These patterns reveal the structure of the particles during assembly.

Toughen up

Other steps in the virus cycle can also be studied. "After they have self-assembled, particles need to toughen up to withstand conditions outside the host cell," says Roos. Other modifications also occur, which prepare the particles to infect other cells. The dynamics of this maturation process are important for our understanding of how viruses work. "And after infecting new cells, the virus particle has to come apart to release

its genetic material."

New technology is now revealing the physical dynamics of viruses. It allows scientists such as Roos and his colleagues to study how genetic material is incorporated and which physical principles guide this process. Most antiviral drugs disrupt the first steps in infection, such as the binding of virus particles to their host cells. Using this new dynamic information, we could develop drugs that block self-assembly or other important steps in the reproductive cycle of the virus.

Nanotechnology

Insight into the physics of virus particles is also important for their use in research, for example as building blocks in nanotechnology or as carriers for antigens in vaccines. Several of the leading COVID-19 vaccines use adenoviruses to deliver the gene for the SARS-CoV-2 spike protein to cells, which then express this gene and consequently generate an immune response. "Understanding how the adenovirus comes together and falls apart could help to create more stable vaccines."

More information: Robijn F. Bruinsma et al, Physics of viral dynamics, *Nature Reviews Physics* (2021). DOI: 10.1038/s42254-020-00267-1

Provided by University of Groningen