Scientists measure energy released from a virus during infection

February 5 2010

Within a virus's tiny exterior is a store of energy waiting to be unleashed. When the virus encounters a host cell, this pent-up energy is released, propelling the viral DNA into the cell and turning it into a virus factory. For the first time, Carnegie Mellon University physicist Alex Evilevitch has directly measured the energy associated with the expulsion of viral DNA, a pivotal discovery toward fully understanding the physical mechanisms that control viral infection and designing drugs to interfere with the process.

"We are studying the physics of viruses, not the biology of viruses," said Evilevitch, associate professor of physics in the Mellon College of Science at Carnegie Mellon. "By treating viruses as physical objects, we can identify physical properties and mechanisms of infection that are common to a variety of viruses, regardless of their biological makeup, which could lead to the development of broad spectrum antiviral drugs."

Current antiviral medications are highly specialized. They target molecules essential to the replication cycle of specific viruses, such as HIV or influenza, limiting the drugs' use to specific diseases. Additionally, viruses mutate over time and may become less susceptible to the medication. Evilevitch's work in the burgeoning field of physical virology stands to provide tools for the rational design of less-specialized antiviral drugs that will have the ability to treat a broad range of viruses by interrupting the release of viral genomes into cells.

Evilevitch's current findings also have the potential to improve the

development of gene therapy, which uses viruses to deliver functional genes directly to human cells to replace defective genes that are causing disease. Gene therapy takes advantage of viruses' modus operandi — injecting genetic material into cells. But instead of forcing in harmful, viral DNA, gene therapy delivers helpful, functional genes. Controlled packaging of the functional genes into the viral delivery system is one of the key factors involved in developing a successful gene therapy.

Many viruses, whether they infect bacteria, plants or animals, are adept at packing long stretches of nucleic acid (DNA or RNA) within their nanometer-sized protein shells. In many of the viruses that contain double-stranded DNA, the DNA gets packaged so tightly that it bends upon itself, resulting in repulsive forces that exert a tremendous amount of pressure on the virus's outer shell, indicating a great amount of stored energy. At the moment of infection, when the DNA is being shot out of the virus, the energy stored in the tightly packed DNA is released and converted into thermal energy.

Evilevitch and his colleagues from Lund University in Sweden, where Evilevitch was previously employed, and the Universite de Lyon in France used an experimental technique known as isothermal titration calorimetry (ITC) to directly measure the heat, and thus the thermal energy, released during viral genome ejection. Until now, only indirect measurements of this energy have been available. They describe this new method in the Feb. 5 issue of the *Journal of Molecular Biology*.

"We are the first group to use titration calorimetry to study genome release from viruses," Evilevitch said. "In this study, we looked at viruses that infect bacteria, called bacteriophages, as an experimental model system, but ITC can also be applied to other types of viruses. We're currently investigating the rotavirus, which causes stomach flu, using our new technique."

In the *Journal of Molecular Biology* report, Evilevitch used ITC to measure the thermal energy released during genome ejection, which is the same as the stored internal energy that results from genome packaging. His results, which agree with analytical models and computer simulations, show that the heat released increases as DNA length increases. He also discovered that the ordering of water molecules around DNA strands inside the virus (called hydration entropy) has a tremendous influence on the build up of energy. This unpredicted effect was not accounted for in the previous models.

"Understanding the energy profile for viral genome release provides information on how to interfere with the process. For example, developing ways to decrease the internal energy in viruses could prevent viruses from ejecting their genome and prevent infection," Evilevitch said.

Provided by Carnegie Mellon University