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Microbiology

Ouch, that needle hurts! How some viruses inject their DNA

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ABSTRACT

Some viruses infect their bacterial hosts by injecting their DNA using a nano-injection machine that resembles a hypodermic needle. They then hijack their host into reproducing new copies of the virus and to unleash those copies to infect other hosts. To understand how this injection machine works in real-time, we developed a model to simulate the injection process.

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Bacteriophage T4 is one of the most common of the viruses that infects Escherichia coli (E. coli) bacteria that serve as the hosts. To accomplish this feat, phage T4 employs a fascinating nano-scale injection machine to first rupture the host's cell membrane and then inject its own DNA into the bacterial host. The viral DNA then commands the host to make many identical copies of the virus. These new virus copies subsequently burst the host (killing it too) and get released into the surrounding environment.

Phage T4 possesses a large (icosahedral) capsid or head containing DNA. This capsid connects to a long and contractile tail by a short neck. The tail ends with a structure called the baseplate that is equipped with long and short fibers, which are responsible for recognizing a host cell and then binding the virus to the host membrane. The tail consists of a hollow tube surrounded by a spring-like sheath. During the injection process, the spring-like sheath contracts significantly, providing the energy and motion to drive the needle-like tip of the tail tube into the host membrane. Indeed, the sheath and tail tube function like a nano-scale hypodermic needle that pierces the cell membrane. The viral DNA within the capsid is then injected into the host through the tail tube.

Although much progress has been made in understanding the structural components of phage T4, little is known about how this fascinating nano-injection machine works in real-time to efficiently rupture the host membrane. Fundamental scientific questions include: 1) how much energy is needed to drive the needle-like tail tube into the host?, 2) what is the required force (and torque) to rupture the host?, 3) what are the mechanisms that dissipate

energy during the injection process?, 4) how does the sheath deform when driving the tail tube into the host?, and 5) what is the time scale of the injection process?

These are exceedingly tricky questions to answer using experimental methods. Since the injection process occurs so rapidly (probably in less than a few milliseconds) and on nanometer length scales, it is merely unobservable using today's imaging methods. So, an alternative way is to build a computational model of the virus and host and to then simulate how the injection process unfolds. However, creating an atomistic-level model for phage T4, composed of millions of atoms, is impossible even using today's supercomputers. Consequently, we took a different track and developed an approximate (continuum-level) model that essentially treats extensive collections of atoms as elastic bodies.

Our method begins by using the elastic rod theory to model each of the (six) rod-like protein strands that form the sheath structure. We add to this sheath model the remaining parts of the virus/host system including the capsid and neck (at the top), the hollow tail tube, and the baseplate and host cell membrane (at the bottom). In particular, we used a viscoelastic model to describe how the cell membrane interacts with the needle-like tip of the tail tube. We estimated the elastic and internal friction properties of the sheath using atomistic modeling (Molecular Dynamic simulation) for a small fraction of the sheath and over a few nanoseconds of simulation time. The resulting multi-scale (atomistic-level to continuum-level) model yields a complete description of phage T4 that can simulate the energetics and dynamics of the injection process.

We learned that the sudden release of elastic energy stored in the (extended) sheath causes the sheath to contract in a "contraction wave" that propagates from the baseplate to the neck. As the sheath contracts, it drives the tail tube into the cell membrane. The needle ruptures the cell membrane using coupled rotation and translation, resulting in significant force and torque on the membrane. The sheath's energy that drives the process is dissipated by several mechanisms and, most importantly, by the fluid friction in the nano-scale gap between the sheath and the tail tube, and by the internal friction in the sheath. The vigorous competition between the driving (elastic) energy in the sheath and the dissipation mechanisms controls the time scale of the injection process. The model further predicts the force needed to rupture the cell membrane.

This dynamic model of T4 provides a significant step forward in understanding how viruses function. Importantly, this advancement arose from the successful combination of virus structural information, physical models, and advanced computer simulation methods. These findings also have implications for designing future bio-inspired drug delivery machines that mimic the highly efficient injection machinery of viruses.