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How Viruses Enter Cells: A Story behind Bacteriophage T4

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Viruses are the most abundant biological agents in nature that need to enter living cells to successfully replicate (1). Although cells are protected by membranes, viruses have developed elaborate mechanisms to overcome this defense. One of the most known and fascinating examples is bacteriophage T4, which infects *Escherichia coli* bacteria (2). The structure of this virus has been well investigated (2–6). It consists of three main parts that are assembled independently and then joined together to produce a mature phage (2). There is a large, multi-protein icosahedral capsid that encapsulates the viral DNA genome. This capsid is coupled via a neck region to a long and narrow tail part, surrounded by a protein sheath. It ends with a baseplate with attached long and short tail fibers, which are responsible for the recognition of specific receptors on the host cell and for binding to the cellular membranes (2–6). The sequence of events that lead to bacterial infection by T4 is also known (3,7). It starts with the virus finding and binding the corresponding receptors on the host cell. After the strong contact is established, the cellular membrane is pierced and the viral DNA is eventually ejected into the host cell. At the same time, the dynamics of virus infection, as well as the energetic and conformational changes in viral particles during these processes, remain not well understood.

It is known that the bacteriophage T4 injection process is associated with a spring-like action of the sheath (2–6). During the contraction, a large conformational change in the sheath takes place. An extended high-energy state transitions into a contracted low-energy state. This leads to simultaneous rotation and translocation of the whole virus structure along the tube tail axis, providing the necessary forces to enter the host cell (4). Several theoretical studies have attempted to evaluate free-energy changes during sheath contraction and produced forces (8,9). But recent advances in experimental studies have provided a significant amount of new information on the properties of bacteriophage T4 viruses, suggesting that a more detailed analysis of virus infection is possible. An article by Maghsoodi et al. (10) in this issue of *Biophysical Journal* presents such an analysis by introducing the first quantitative theoretical model that describes the dynamics and energetics of the phage injection machinery.

Maghsoodi et al. (10) developed an elegant theoretical method to capture the dynamic and energetic properties of bacteriophage T4 during the injection process. Because the entire T4 injection machinery is too complex to be fully described at the atomistic level for realistic timescales, a two-state modeling process has been employed. First, using known protein structures, a segment of the sheath is interrogated using full-atomic MD simulations. Then, the elastic properties of the sheath are evaluated from equilibrium fluctuations of the corresponding geometric parameters. In the second stage, a continuum model of the sheath that utilizes the calculated elastic properties is built. Furthermore, this elastic structure is coupled with other parts of the virus (capsid, neck, and tail-tube regions), approximating them as rigid bodies. This hybrid procedure allows Maghsoodi et al. (10) to describe and analyze the injection dynamics of T4 viruses. It was found in the computational model that the injection process is quite fast, taking only a few microseconds to pierce the cellular membrane, but because the cellular membrane has not been taken into account in this model, the realistic injection time most probably will be slower due to interactions between the virus and the membrane. The developed theoretical model also revealed details of the mechanical changes in the T4 bacteriophage. It turns out that the sheath first quickly translates, which is followed by slower rotation of the virus. Furthermore, it was suggested that this two-punch combination of

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translation followed by rotation might provide the most efficient mechanism for breaking the cellular membrane. In addition, Maghsoodi et al. (10) evaluated the energetics of sheath contraction. They found that the injection process is driven by ~5500 kT internal energy, which corresponds to a maximal piercing force of 860 pN. These predictions fully agree with experimental estimates and known theoretical bounds (8,9).

Although the work of Maghsoodi et al. (10) is successful in providing a quantitative description of the injection process for T4 viruses, one should note that there are several issues with this approach. The most serious problem is that the cellular membranes are not taken into account in the computational model. One could expect that interactions between the membrane and the viral parts might strongly affect the injection dynamics and energetics. The theoretical model also considers the capsid, neck, and tail tube of the phage as rigid objects, whereas in reality, these components probably are more flexible. It is also important to note that the cellular membrane piercing discussed by Maghsoodi et al. (10) is followed by the more complex and also not-well-understood process of DNA genome ejection (11). Despite these issues, the work of Maghsoodi et al. (10) is a large step forward in our understanding of how viruses function. The most valuable part of this work is quantitative predictions that can be tested in experiments. This is also an example of successful combination of the structural information, realistic physical models and advanced computer simulation methods for analyzing complex biological phenomena.

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