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Structural Modeling of Biological Entities, Such as Viruses, At Atomic Resolution

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Abstract

The structural modeling of biological entities, particularly viruses, at the atomic level is a noteworthy pursuit in the field of molecular biology. This endeavor necessitates the application of advanced computational techniques to elucidate the three-dimensional structures of these entities at the molecular level, thereby providing insights into their functioning and interactions with other biological components. The results of such studies hold immense potential for enhancing our understanding of the fundamental mechanisms governing biological processes and informing the development of novel therapeutic strategies. The achievements in question were realized through the utilization of UCSF Chimera, a software program for molecular visualization. These accomplishments include the investigation of T bacteriophages and other bacterial infection models. To attain this level of detail, X-ray structures and cryo-EM maps sourced from the RCSB (Research Collaboratory for Structural Bioinformatics) and EMDB (Electron Microscopy Data Bank) databanks were employed in conjunction with a high-performance computer to construct structures comprising millions of atoms.

Introduction

The construction of structural models for complete viruses has been hindered by the enormous size of these structures, which consist of millions of atoms and can only be handled by supercomputers, as well as the lack of availability of all the structures that make up the complete virus. However, these challenges can be overcome by utilizing high-performance computers and employing Alpha Fold [1] for proteins that do not have determined structures. Recently, a structural model of bacteriophage T4 was successfully constructed [2] (Figure 1), demonstrating the feasibility of this approach. Moreover, other structures such as *Escherichia coli* infection models of bacteriophage T7 and other viruses (Figures 2 to 4) can also be built.

The development of structural models for T-bacteriophages has been accomplished [3]. These organisms are of historical and essential significance, as they aid in elucidating biological functions. The construction of the bacteriophage T4 was achieved through the use of the UCSF Chimera software [4] and pdb and emdb files available in the databanks. These files consist of over 6 million atoms, representing the most detailed reconstruction of the entire organism to date. The head, tail, and tail fiber structures have been described in various research articles over the past 20 years, and using cryo-EM density maps as guides, each protein structure was fitted to build the entire structure. The entire virus was approximately 95% complete, with structures determined at atomic resolution.

Figure 2 displays the structural modeling of *Escherichia coli* cells measuring 2-3 microns in length upon infection with bacteriophage t7. For further information regarding the structural modeling of bacteriophage t7, refer to [5].

Figure 3 depicts the recently published structure of crass virus, which is prevalent in the human gut. This figure illustrates the long tail fibers, which were added through structural modeling.

Lastly, Figure 4 demonstrates the structural model of *Shigella flexneri 6*, highlighting the utility of structural modeling in analyzing structure-function relationships and elucidating various biological mechanisms, such as genome packaging, head assembly, genome ejection, and infection attachment to bacterial cells.

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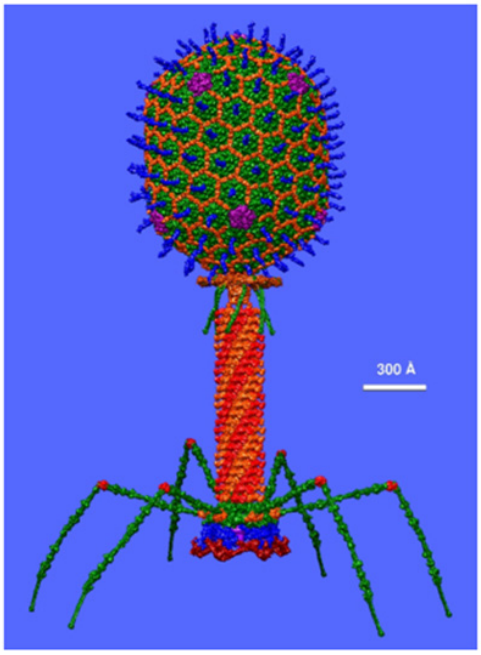

Figure 1: Structural Model of Bacteriophage T4.

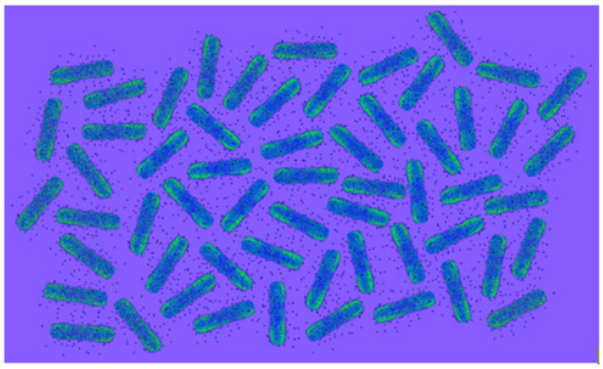

Figure 2: Bacteriophage T7 Infection of E. coli Structural Model.

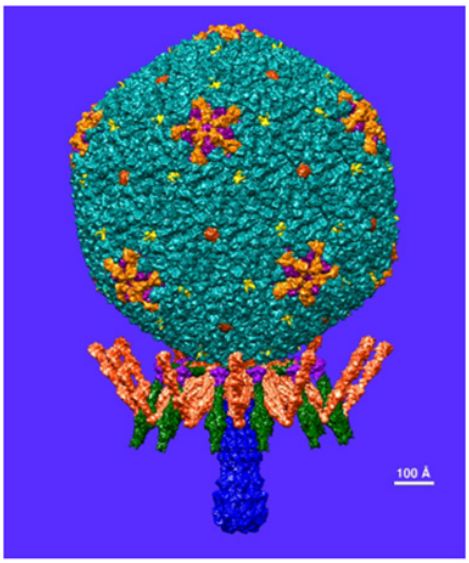

Figure 3: Crass Virus Structural Model.

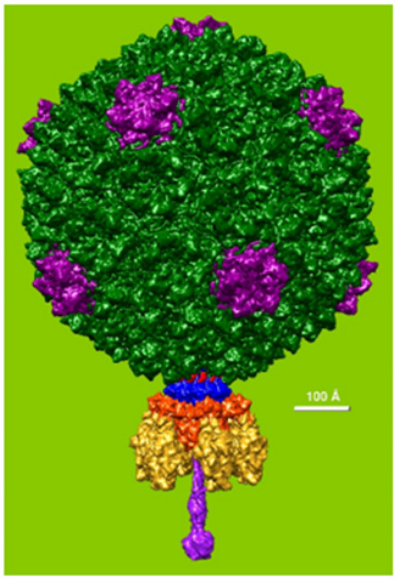

Figure 4: Structural Model of Bacteriophage SF6.

With atomic resolution, the individual atoms on the computer screen are visible and can be analyzed at the residue level, providing substantial information for mutagenesis analysis to determine the functions of specific domains of individual proteins and residue-residue interactions that explain the behavior of different proteins in various locations. The knowledge of specific amino acid functions enables researchers to manipulate proteins with the ultimate goal of utilizing viruses to achieve specific functions that are not naturally occurring, such as employing bacteriophage display technology for vaccine development or using the genome packaging machine to introduce desired genes inside cells for therapeutic purposes. Furthermore, structural models are highly beneficial for educational purposes at every level, from high school to university, facilitating the teaching and research of crucial aspects of biology at atomic resolution that are not visible through any light, electron microscope, or other method.

Molecular dynamics is a valuable tool for examining protein-protein interactions by simulating the movement of proteins on a computer. While simulations of this nature have traditionally been limited to a few nanoseconds, recent advances have allowed for simulations of up to several nanoseconds for complexes consisting of up to 50,000 to 100,000 atoms. These simulations require significant computational power, and may take several days to run on a high-performance computer. The most commonly used software for molecular dynamics simulations is Nanoscale Molecular Dynamics (NAMD) [6], which can be operated using Visual Molecular Dynamics (VMD) software [7]. For larger complexes, access to a supercomputer may be necessary, which can typically be accessed online after a researcher makes a request.

Conclusion

In the year 2023, structural modeling has fulfilled a long-standing aspiration of structural biologists, which was to obtain the structures of complete organisms. The simplest organism is a virus, followed by cells. Although some researchers have begun to model entire cells, their resolution is currently low. In order to achieve atomic resolution models of entire cells, we will need to await further advances in computational power, which are expected to be realized in the next decade through breakthroughs in computer development. Nonetheless, we will continue to push the boundaries of scientific research in pursuit of these objectives.

Conflict Of Interest

The author declares no potential conflict of interest.

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