



Editorial overview: Virus structure and expression

Juliana Reis Cortines and Peter Prevelige Jr

Current Opinion in Virology 2019, 36:iii–v

For a complete overview see the [Issue](#)

Available online 25th June 2019

<https://doi.org/10.1016/j.coviro.2019.05.012>

1879-6257/© 2019 Published by Elsevier B.V.

Juliana Reis Cortines¹

¹ Department of Virology, Microbiology Institute, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil
e-mail: cortines@micro.ufrj.br

Juliana Reis Cortines is an Associate Professor in the Institute of Microbiology at the Federal University of Rio de Janeiro. She received her PhD in Biochemistry at the Federal University of Rio Janeiro studying the folding thermodynamics of HIV capsid protein. She then moved on to her postdoctoral studies in Professor Peter Prevelige's laboratory at the University of Alabama at Birmingham, researching the structural features of HIV capsid maturation. Her next postdoctoral was under Professor Carolyn Teschke at the University of Connecticut. Her goal was to understand the scaffolding protein-driven assembly mechanism of bacteriophage P22. Her research now focuses on the application of P22 as a nanomaterial and the structural studies of giant viruses.

Peter Prevelige Jr²

² Department of Microbiology, University of Alabama at Birmingham, UK

Peter Prevelige is Professor of Microbiology at the University of Alabama at Birmingham. He received his PhD in Biochemistry at Brandeis University studying the structural effect of histone acetylation under Professor Gerald D. Fasman, and carried out postdoctoral work on bacteriophage assembly at MIT under Professor Jonathan King. His main research interests lie in biological self-assembly, with particular focus on elucidating the assembly pathways that lead to properly dimensioned viral capsids.

Humans are curious by nature. Discoveries are made by observation and effort, starting with the creation of the wheel. Observation was also key to the development of vaccines by Edward Jenner in the XVIIIth century, when he used 'attenuated' cow smallpox to immunize the French population.

The term 'virus' would be coined approximately a century later, with the independent and groundbreaking work from Iwanowski and Beijerinck. They showed that a filtrate of infected material could generate disease on previously healthy tobacco leaves. A few decades later, the Tobacco Mosaic Virus became the first virus to have its structure determined by X-ray crystallography, giving Wendell Stanley the Nobel Prize in 1946. It was also a landmark for the beginning of the structural virology field, and its history is extensively reviewed [1].

Driven by the scientific method of: observation, hypothesis, and experiment, structural virology took a leap with the development of several crucial techniques such as mass spectrometry, electron and cryo-electron microscopy. In the present Current Opinion of Virology issue, we sought to display major advances in describing the three-dimensional structures of viruses, including their assembly pathways.

Viruses are mostly known as disease-causing agents, which pose a significant burden to humanity. Modern epidemics can be exemplified by HIV and arthropod-borne diseases, such as dengue, yellow fever, and Zika. All viruses must follow a few steps in order to induce the production of infectious progeny by their hosts. In humans, more often than not, contact with viruses induces an immune response that results in viral clearance. On the down side, the consequences of ridding the organism of a pathogen may generate significant deleterious effects as observed for example during Flavivirus infections. Having very similar capsid structures, Dengue viruses 1, 2, 3 and 4 induce the production of non-interchangeable neutralizing antibodies, which can cross-react with other Flaviviruses, leading to potentially serious hemorrhagic episodes through a process called antibody-dependent enhancement (ADE). Understanding of the molecular mechanisms accounting for this phenomenon is growing due to a combination of cellular and structural biology. As shown by [Morrone and Lok](#), the orientation of antibody binding to viral proteins and the maturation state of Dengue virion are intimately related to ADE. Thus, understanding the structural dynamics of antibody binding may aid in the production of efficient vaccines against diseases that can potentially affect 390 million people across the globe.

Maturation is also a key structural divider in HIV infection. The human immunodeficiency virus is the causative agent in AIDS, being recognized as

such in the 80s. At that time, it was known as a death sentence. It was one of the major driving forces for the development of rational drug design, which placed structural virology on the spot. Major advances were made to the extent that anti-viral drugs were approved for human treatment and now, being HIV positive is more of a chronic disease. The AIDS cure is moving forward; however, it is a still far horizon. A major concern is to understand why and how, during its infection cycle, HIV goes through a maturation step requirement for infectivity. In this issue, the reader can find a thorough review on the structural aspects of HIV maturation. The complex transition in capsid protein required for HIV infectivity sheds light on the biology of capsid protein itself and in viral life cycle aspects such as viral enzyme functions, viral budding and RNA recognition.

Even though the above examples cause unrelated diseases, they and the vast majority of viruses with known structure (~70%) [2] display a form of icosahedral symmetry. Viral capsids, as theorized by Caspar and Klug in 1962 (and confirmed by many others on the next half century), tend to be extremely regular upon assembly. A striking feature that may be partly responsible for such periodicity is the overall conservation of capsid protein folds: even though amino acids conservation is not a requirement, viral proteins assume common topologies, such as the HK97 fold, explored in this issue by [Duda and Teschke](#). The existence of common folds in capsid proteins suggests they evolved divergently from multiple origins to create their genome-protecting capsids. The conserved domain organization of capsid proteins helps us understand how capsids assemble and the role of each protein domain. In the HK97 fold, for example, inter-capsomer and intra-capsomer interactions govern the size and the maturation state of the capsids.

The astonishing regularity of such capsids have been studied by scientists for decades. Advances in cryo-electron microscopy are revealing that strict adherence to symmetry is not a requirement for virus assembly. For the longest time, the determination of virus capsids' high-resolution structures imposed the icosahedral symmetry to increase the resolution obtained. By doing so, details on capsid assembly were lost. As pointed out by [Goetschius et al.](#), local asymmetry is a necessary part of capsids. These structural features may be required in crucial biological roles, that is, genome packaging and protein:protein interactions, such as rearrangements during capsid maturation. In addition, asymmetries can be crucial for icosahedral viruses to accomplish several steps in a virus' life cycle that up to now were unknown.

Significant advances in mass spectrometry have shown great potential in providing information on capsid mass measurements, detection of assembly intermediates and antibody:viral protein interactions. As [Ashcroft's](#) review

makes clear, in order to assemble a symmetric capsid, different intermediates may be formed, depending on the viral system and experimental conditions. Once assembled, viral proteins may undergo extensive glycosylations, which are crucial for antigenic responses, as reviewed by [Hargett and Renfrow](#). In both mass spectrometry reviews, authors cite the importance of structural studies to understand and prevent virus infections.

Mass spectrometry is also being used to analyze the proteome of newly discovered giant viruses. Prospection of ~300 virus isolates demonstrated that their capsids have sizes ranging from hundreds of nanometers to few micrometers. Their genomes hold information for an average of 900 proteins. Additional microscopy techniques have jump-started the analysis of complex structures that do not strictly follow the icosahedral symmetry rules. [Boratto et al.](#) describe the most recent advances in the structural biology of Tupanviruses the most complete and complex members of the virosphere. On this same premise, viral capsomer organization can generate oddly shaped capsids, such as the ones observed in the archaeal viruses and reviewed by [Hartman et al.](#) Archaeal viruses evolved under the pressure of extremely hostile environments, which resulted in unique features such as high degree of glycosylation and capsid proteins with extensive hydrophobic interactions.

In recent years, an interesting twist was taken when researchers started viewing viruses not as "bad news wrapped in proteins" (Peter Medawar). Viruses, in most cases, target specifically permissive cells to deliver their genome via specific viral:host protein:protein interactions. Therefore, once the assembly properties and conditions of a certain virus is known, it could be used in theory as a nanocompartment for targeted molecule delivery, exemplified by their genomes. At this point, we can change our perception on these pathogenic entities and view them as molecular nanomachines. For example, in bacteriophages and some animal viruses, the genome is packaged via a molecular motor often called portal protein complex. These complexes are capable of exerting a power density twice the generated by man-made automobile engines [3]. That force is necessary to package DNA into capsids to a near-crystalline density, which, as described in [Jardine's](#) review, must accommodate several physical constraints, only observed in portal containing viral capsids. These discoveries have been opening new views on such systems and providing new insights into biophysical properties of macromolecules.

Another relatively new area of research is the use of viruses as tools for nanotechnology. They fulfill many requirements needed for the successful construction of nanomaterials. They self-assemble readily and consistently into biodegradable containers, amenable to modifications in their interior and/or exterior. [Selivanovitch and Douglas](#)

navigate through several examples on the usage of viruses as functional nanomaterials and their applications from biophotonic crystals to nanoreactors.

The quest and curiosity to understand these nature's nanomachines perfected by evolution lead us to compile the reviews presented in this issue. As we were preparing this Overview, we learned of the passing of Michael Rossmann. Professor Rossmann's contributions to structural biology, and structural virology are legendary. Using X-ray crystallography and more recently cryo-electron microscopy he solved important virus structures ranging from the smallest picorna viruses through to the giant viruses. His energy and enthusiasm for structural virology were as inexhaustible as his

contributions to structural techniques, virus structure, and biological insights were seminal. The community will miss his insight, wit, and scientific contributions greatly.

References

1. Rossmann M: **Structure of viruses: a short history.** *Q Rev Biophys* 2013, **46**:133-180 <http://dx.doi.org/10.1017/S0033583513000012>.
2. Krupovic M, Koonin EV: **Cellular ancestors of viral capsids.** *Proc Natl Acad Sci U S A* 2017, **114**:E2401-E2410 <http://dx.doi.org/10.1073/pnas.1621061114>.
3. Chemla YR, Smith DE: **Single-molecule studies of viral DNA packaging.** In *Viral Molecular Machines. Advances in Experimental Medicine and Biology*, , vol 726. Edited by Rossmann M, Rao V. Boston, MA: Springer; 2012 http://dx.doi.org/10.1007/978-1-4614-0980-9_24.