Preface

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Published in:
Journal of Physics-Condensed Matter

DOI:
10.1088/1361-648X/aacb6c

PREFACE

Special Issue on the Physics of Viral Capsids

IOP Publishing Journal of Physics: Condensed Matter
J. Phys.: Condens. Matter **30** (2018) 290201 (3pp) https://doi.org/10.1088/1361-648X/aacb6c

Preface

Special Issue on the Physics of Viral Capsids

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In the late 19th century infectious disease research started to shape up. These developments were further catalysed after the publication in 1898 by Martinus Beijerinck from the Polytechnische School in Delft (now Technische Universiteit Delft) about a *contagium vivum fluidum* [1]. He was the first to show and realize that there must be a new type of infectious agent, smaller than bacteria, that is able to reproduce in infected organisms [2]. With his publication the field of virology was born. The *contagium vivum fluidum* that was discovered is the tobacco mosaic virus (TMV), responsible for brownish spots on tobacco leaves. Crystallography and electron microscopy (EM) studies in the 1930s revealed that TMV is a rod-shaped aggregate. These experiments, where physics techniques were used to study viruses, are early examples of research in the field that is now known as physical virology. After the discovery of TMV a multitude of other viruses were discovered, infecting archaea, bacteria, plants and animals.

The protein shell that surrounds the genome of many viruses is known as a capsid (in Latin, *capsa* means a box) and can have all sorts of shapes, though the most common shape is icosahedral [3]. In addition to the capsid, a variety of eukaryotic viruses also possess a lipid envelope, which is essential for successful interactions with the host cell. Interestingly, mechanical, thermal, morphological and biological properties differ a lot between viruses, depending on the nature of the proteins (and sometimes lipids), of which the virus has self-assembled. This makes it especially interesting as objects of study to biophysicists, both from experimental and theoretical perspectives. With the advent of advanced modelling approaches, high resolution electron and atomic force microscopy (AFM) techniques, native mass spectrometry and advanced fluorescence microscopy approaches over the last ~25 years, the field of physical virology has made a tremendous development. This was catalysed by the steady increasing input of physicists to describe virological features in a quantitative manner. This special issue provides a survey of current biophysical research in this area.

Despite decades of studies on viral self-assembly and disassembly these essential steps in the viral life cycle remain poorly understood and a number of groups are working on these issues to attempt to finally elucidate the physics behind (dis)assembly. Temperature induced disassembly of cowpea chlorotic mottle virus (CCMV) was scrutinized by small angle neutron scattering and analysed using lattice models [4], whereas the influence of RNA on assembly was studied using self consistent field theory [5], coarse-grained molecular dynamics [6] and polymer field theory [7]. In this latter study it was demonstrated that there are preferences for a capsid to encapsulate linear RNA as opposed to highly branched genomes and this is explained in terms of a difference in stiffness. RNA encapsulation was also studied in terms of the spatial compactness of the viral genome. In particular this was analysed for phage MS2 and brome mosaic virus by comparing compactness of wild type genomes with that of mutated ones [8]. EM experiments were performed to explore possibilities to encapsulate cargo into infectious bursal disease virus using an *in vitro* assembly/disassembly system [9]. A related EM study focused on the impact of the length of the encapsulated oligonucleotide cargo on the stability and structure of alphavirus particles [10]. Furthermore, Förster resonance energy transfer was applied as a strategy to study the assembly of CCMV viruses without labelling the exterior of viruses, but by using fluorescently labelled DNA oligomers [11]. These publications show that in a variety of recent assembly/disassembly studies the influence of cargo is a main theme.

1361-648X/18/290201+3$33.00

Bozic and Podgornik [12] analyze the electrostatic signature of viruses theoretically and show that N-terminal disordered tails of the capsid proteins, responsible for aggregation of the proteins around the nucleic acids, stay positively charged even at very basic pH values. The pH dependent stability of norovirus-like particles has been explored experimentally using native mass spectrometry and EM by Pogan *et al* [13]. These latter studies are part of the wider research effort to study stability and mechanical properties of viruses. In this regard, Dharmavaram *et al* [14] argue that the capsids of certain archaea-infecting viruses are in a smectic liquid crystalline state in which they can undergo large shape transformations while remaining stable against rupture by osmotic pressure. Using AFM, the issue of virus stability after desiccation was scrutinised, focusing on the role of the genome and structural ions to keep triatoma virus in shape [15]. A 'virtual AFM' for numerical studies of AFM nanoindentation has been proposed by Aznar *et al* [16], whereas 'TensorCalulator' was used to predict stress distributions in indented CCMV particles [17], a virus that serves as model system for a variety of physical virology approaches.

Finally, viral budding as well as viral fusion has been studied. Membrane vesiculation by dengue virus proteins was scrutinized, whereby residues were identified that lead to essential membrane bending stress [18]. Influenza virus fusion with the host cell membrane was scrutinised in a single-particle approach [19]. Using total internal reflection fluorescence microscopy it was demonstrated that the composition of the membrane exerts a major impact on the process.

This collection of recent work covering the physics of viruses and their capsids illustrates the fast developments in which the physical virology field moves forward. While we are increasingly better understanding viral (dis)assembly and mechanics, there remain large gaps in our knowledge. We also notice that physicists additionally turn to more complex systems by introducing and studying the effects of the lipid envelope surrounding some viruses. Overall we expect a further increase in physical virology studies in the years to come, as the power of this approach is increasingly being recognised.

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