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Viral biophysics special issue: Advances in modeling viruses open new therapeutic avenues

RNA viruses cause numerous infectious diseases ranging from COVID-19, dengue, Zika, and influenza to chronic maladies such as HIV and hepatitis C. These RNA viruses and other pathogens are most likely to cause further pandemics. Most current antiviral strategies target viral proteins; however, the high mutation rates of most viral proteins allow them to escape therapeutics. Alternative targets, such as conserved functional RNA elements, allosteric sites, and transient intermediates, are therefore actively studied as novel antiviral strategies. Exploiting such targets relies on mapping the structure-function relationship across scales from the conformational ensembles of individual RNA elements, via the large conformational changes of fusion proteins, to the assembly of viral capsids. Building biophysical models using experiments and simulations allows us to build these connections. Numerous challenges complicate these efforts and attract significant research attention. These include the heterogeneity and dynamics of RNA structural ensembles, the scale of whole virions, developing reliable physically accurate coarse-grained representations, and accounting for the electrostatics of charged RNA viral genomes.

This special issue of *Biophysical Journal* grew out of the CECAM workshop "Biophysical modeling of the structure and function of viruses" that we organized at the Institut d'Études Scientifiques de Cargèse, Corsica, in October 2025. The workshop brought together researchers working on viral biophysics at various scales with contributions from experiments and simulations combining virology, structural biology, statistical physics, chemistry, and computer science (Figure 1). The contributions in this special issue reflect this interdisciplinary range, which we believe is essential for studying the emergent phenomena observed across scales in viral biophysics. They range from sequence-level analysis of viral genomes to simulations of entire capsids and the *in vitro* reconstruction of enveloped particles; they combine computational, theoretical, and experimental approaches.

Two contributions address viral RNA at the level of sequence and secondary structure. Wang et al. present VARIANT, a web server for mutational analysis of RNA viral genomes that handles both single- and multi-segment genomes.[1] Beyond standard annotation of point mutations, insertions, deletions, and frameshift events, VARIANT detects "row" and "hot" mutation patterns and potential programmed ribosomal frameshifting regions. It also classifies the topologies of frameshifting element structures (FSEs) with dual graphs. Precomputed analyses are included for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), HIV-1, influenza H3N2, Ebola virus, and chikungunya virus, and users can upload other genomes. Hozumi et al. address a known limitation of minimum free energy (MFE) secondary structure prediction, which can miss helices in known structures.[2] By partitioning the space of multiloop initiation and branching parameters, their approach allows enumeration of distinct optimal structures, improving on MFE predictions.

Programmed −1 ribosomal frameshifting is a recurring theme in this issue. Compact viral genomes use it to expand their protein repertoire and to balance the stoichiometry of viral proteins. In their review, Portillo-Ledesma et al. introduce frameshifting mechanisms and review open questions.[3] They describe how coarse-grained graph representations, mutation design, all-atom molecular dynamics (MD), and enhanced sampling have been combined with chemical mapping and functional experiments to probe frameshifting mechanisms. Their three examples are the FSEs of SARS-CoV-2, HIV-1, and chikungunya virus. A central theme is the structural plasticity of the FSE, which can adopt alternative folds. Malekzadeh et al. examine this plasticity at atomistic resolution.[4] They use enhanced sampling to study interconversions between two three-stem H-type pseudoknots, motifs 3_3 and 3_6, of the 87-nt SARS-CoV-2 FSE, revealing differences in the forward and backward pathways.

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Figure 1. Group photo taken on an excursion to Punta Omigna near Cargese as part of the CECAM workshop on "Biophysical modeling of the structure and function of viruses."

Two further contributions show how RNA dynamics shape recognition and catalysis. Samant et al. simulate TAR RNA from HIV-1, HIV-2, and bovine immunodeficiency virus, both without and with bound Tat.[5] They identify the bulge and the apical loop as allosteric hubs: the bulge engages Tat, while the loop interacts with cyclin T1. HIV-1 TAR relies on an induced-fit mechanism, while HIV-2 TAR favors conformational selection. Self-cleaving RNAs play roles in viral RNA replication and RNA splicing. Among them, the hairpin ribozyme has a catalytic mechanism that has been debated for more than two decades. Forget and Stirnemann use Hamiltonian replica exchange simulations to map active-site ensembles for several protonation states along three candidate mechanisms.[6] Their simulations suggest key differences between candidate pathways, paving the way for deciphering the exact mechanisms in the future.

Allosteric effects also determine the behavior of viral proteins. Dutta and Voth use atomistic MD simulations of Delta and Omicron SARS-CoV-2 spike proteins with and without ACE2.[7] ACE2 binding markedly strengthens allosteric coupling throughout the spike. The authors propose that the N856K and T547K mutations reshape the conformational landscape of Omicron, and they relate the variant-specific couplings to differences in fusogenicity and immune evasion. Sanlley Hernandez et al. combine microsecond MD simulations with dynamical network analysis to study the SARS-CoV-2 main protease (M^{pro}).[8] They simulate monomers and dimers, each either without ligand or bound to a natural peptide substrate, the covalent inhibitor nirmatrelvir or the noncovalent inhibitor ensitrelvir. Dimerization leads to strongly correlated motions in the interface between domains II and III, with domain III acting as an allosteric switch. Ensitrelvir-bound monomers adopt a dimer-like network, which the authors suggest may act as an inhibitor to dimerization. Together with the TAR study,[5] these papers show how single mutations or binding events can reroute long-range communication in both viral RNAs and viral proteins, pointing to new druggable sites.

Viral entry involves large conformational changes and membrane remodeling. Kulshrestha et al. use a coarse-grained structure-based model with an implicit membrane to study the prefusion-to-postfusion transition of the SARS-CoV-2 spike S2 subunit.[9] They identify the transmembrane domain as a potential regulator of spike-mediated fusion kinetics. Anika et al. measure lipid mixing between single dengue virus-like particles and tethered liposomes and interpret the data with kinetic models.[10] The pH dependence of fusion kinetics can only be explained if the mechanism contains an off-pathway state. For at least some virions, this state appears slowly reversible over tens of minutes. The findings suggest that an off-pathway state may be a general feature of flavivirus fusion. Nonenveloped viruses instead rely on the release of membrane-active peptides from the capsid. Carten and May develop a structure-based MD framework for the entire $T = 3$ Flock House virus capsid, including a low-pH capsid model of the whole capsid.[11] Their results show how capsid geometry, symmetry, and environment together control peptide release.

Two experimental studies address viral assembly and envelopes. Mandal et al. use *in vitro* model membranes and quantitative fluorescence microscopy to examine how lipids affect the hepatitis C virus core protein, which forms the viral capsid.[12] Interactions with anionic phospholipids affect binding of the core protein to both monolayers and bilayers. L-α-phosphatidylinositol-4-phosphate enhances its multimerization and might thereby drive lateral assembly toward capsid formation. The core protein in turn measurably changes the biophysical properties of the membrane. Duran-Meza et al. take an engineering perspective.[13] Their starting point is the capsids of two nonenveloped plant viruses, cowpea chlorotic mottle virus and brome mosaic virus. They show *in vitro* that intact capsids can be wrapped in lipid bilayers whose composition is chosen to match the capsid charge. Such enveloped virus-like particles are a first step toward combining the robustness and scalability of plant virus capsids with the functional advantages of lipid envelopes for RNA delivery and vaccine design.

Taken together, the papers in this issue highlight several themes. First, biomolecular function is increasingly described as a result of ensembles and alternative states rather than single structures. Examples are alternative secondary structures,[2] competing pseudoknot folds,[3,4] protonation-dependent active-site ensembles,[6] and off-pathway fusion states.[10] Second, single mutations and binding events can rewire allosteric communication in viral RNAs and proteins.[5,7,8] Third, potential intervention points extend beyond canonical binding sites. They include conserved RNA elements, the spike transmembrane domain, allosteric networks, and fusion intermediates. Fourth, the most informative models are closely tied to experiment. Examples include kinetic models fitted to single-particle data,[10] simulations combined with chemical mapping,[3] and simulated intermediates compared with cryo-electron microscopy structures.[9]

We hope that this issue will serve both as a showcase for current state-of-the-art research in viral biophysics and as a means to further drive interdisciplinary studies of viral biophysics toward a better understanding of viruses and novel therapeutic approaches.

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