Highlights

Molecular dynamics of the viral life cycle: Progress and prospects

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- Molecular dynamics simulations are the central technique uniting the field of computational virology
- Viruses responsible for recent epidemics and pandemics have been the focus of computational studies
- Advanced simulation techniques are being applied to characterize the dynamics of viral life cycle processes
- Integrative modeling and simulation approaches are enabling construction of intact extracellular virions
- Computational studies of viruses are realizing greater complexity, higher resolution, and longer timescales

Molecular dynamics of the viral life cycle: Progress and prospects

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ABSTRACT

Molecular dynamics (MD) simulations across spatiotemporal resolutions are widely applied to study viruses and represent the central technique uniting the field of computational virology. We discuss the progress of MD in elucidating the dynamics of the viral life cycle, including the status of modeling intact extracellular virions and leveraging advanced simulations to mimic active life cycle processes. We further remark on the prospects of MD for continued contributions to the basic science characterization of viruses, especially given the increasing availability of high-quality experimental data and supercomputing power. Overall, integrative computational methods that are closely guided by experiments are unmatched in the level of detail they provide, enabling—now and in the future—new discoveries relevant to thwarting viral infection.

1. Introduction

Viruses are ubiquitous infectious pathogens, representing the most abundant biological entities on the planet [1]. They are highly diverse in form and function and affect all six kingdoms of life. Structurally, viruses are complex molecular machines, highly evolved to infiltrate their hosts and manipulate them in order to reproduce. Although the details vary significantly across systems [2], the viral life cycle generally includes the processes of cell attachment and entry, delivery and replication of genome, assembly and maturation of progeny, and release from the host cell to propagate infection (Figure 1). Investigation of viruses and their life cycle processes is an active area of research, both in terms of basic science characterization and drug and vaccine development. The overarching goal of most studies, from a disease treatment and prevention perspective, is the realization of strategies by which viruses can be thwarted, their life cycles interrupted.

Molecular dynamics (MD) simulations have emerged as an essential computational technique for the examination of viruses. Highly complementary to experimental approaches, MD simulations can reveal structural and dynamical details that may not be otherwise accessible, both guiding experiments and facilitating interpretation of their findings. Recent reviews have discussed the burgeoning field of "computational virology," in which simulations across a range of spatiotemporal resolutions are applied to viruses [3, 4, 5, 6]. Due to calculation expense, atomistic MD simulations have primarily explored individual components of viral systems [4], particularly at equilibrium, to establish chemical-physical properties. While mechanistic details of viral life cycle processes can sometimes be inferred from such studies, technological progress in MD codes and supercomputing resources are enabling more comprehensive virus models and advanced simulations of processes in-action, revealing new insights into stages of the viral life cycle. Here, we highlight exemplary simulation work paving the way for deeper understanding of virus biology and consider the future of computational virology in light of recent developments.

2. Host cell attachment and entry

From the perspective of the host, the viral life cycle begins with recognition and attachment to receptors on the cell surface (Figure 1, step 1). Often, glycoproteins displayed on the virion mediate the process of receptor binding. All-atom simulations have been widely applied to investigate viral glycoproteins complexed with their respective receptors [4], with particular focus on influenza A hemagglutinin (HA) and human immunodeficiency virus 1 (HIV-1) envelope (Env) protein. Much recent work has investigated cellular adhesion of the novel coronavirus (SARS-CoV-2) spike (S) protein, which must undergo a closed-to-open conformational transition to expose the receptor binding domain.

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All-atom steered MD mimicking the transitions suggested that the closed state is heavily stabilized by interdomain interactions and that the open state is likely transient [7]. It was observed that S can access a semi-open intermediate state via thermal fluctuations to lower the barrier for the full opening transition; the semi-open state appears capable of ACE2 receptor binding and may play a role in recognition. Microsecond all-atom simulations of wild-type S versus the now widespread D614G mutant indicated an increased propensity for the latter to adopt the open conformation [8], providing an explanation for increased receptor binding and infectivity. MD of glycosylated S revealed that viral glycans may modulate the conformational dynamics associated with the closed to open transition [9], in addition to protecting it from antibody recognition [10] and premature proteolytic cleavage [11]. Atomistic simulations further investigated the complex between S and the full, membrane-embedded ACE2 receptor, revealing the potential for the glycoprotein to bind multiple copies of the receptor upon cell attachment [12]; the notable flexibility observed for ACE2 was proposed to influence conformational changes in bound S that facilitate fusion of the viral and host membranes.

The process of membrane fusion, essential for cell infiltration in enveloped viruses (Figure 1a, step 1), represents another key focus of computational investigation. Often, the same glycoproteins that mediate attachment also catalyze fusion. The most widely studied viral fusion protein is HA [13], which undergoes acid-dependent conformational rearrangement, inserts a newly-exposed hydrophobic peptide into the host membrane, and acts cooperatively with additional copies of HA to bring the viral membrane within proximity to fuse. Constant pH simulations of HA were used to investigate the early stages of conformational change, establishing the protonation states of titratable residues as the environment was acidified [14]. Equilibrium MD at low pH revealed preliminary dissociation of the globular head domain and emergence of the fusion peptide in response to disrupted hydrogen bonds. Further all-atom simulations employed a combination of unbiased and umbrella-biased sampling with simulated tempering to mimic the loop-to-coiled-coil transition that drives HA's ultimate exposure and placement of the fusion peptide [15]. Calculation of free energy profiles indicated that the conformational change is not a downhill process, suggesting an alternative to the long-held hypothesis of a "spring-loaded" mechanism.

Atomistic self-assembly simulations initiated from a random configuration of protein and lipids were used to predict the interaction of the HA fusion peptide with a model membrane bilayer [16]. Both membrane-spanning and interfacial conformations of the peptide were observed, with the former exhibiting key determinants for membrane fusion, including reduced bilayer thickness and increased disorder and protrusion of lipid tails. The complete fusion mechanism was investigated based on simulations of a proteoliposome embedded with full-length, pH-activated HAs interacting with a planar bilayer [17]. Atomistic models revealed the role of HA in promoting lipid tail protrusion and formation of the fusion stalk at the proximal membrane leaflet; coarse-grain models demonstrated the role of HA in recruiting the distal membrane leaflet into the stalk, followed by formation and opening of the fusion pore.

Beyond HA, MD simulations have also been recently applied to study the proteins responsible for membrane fusion in Ebola virus, Chikungunya virus, and vesicular stomatitis virus [18, 19, 20]. However, computational investigation of viral entry is not limited to enveloped viruses. Recent work on the non-enveloped Flock House virus (FHV), which releases lytic peptides to escape the endosome (Figure 1b, step 1), employed atomistic simulations at neutral and low pH to reveal acid-dependent opening of the five-fold capsid pores [21]. Steered MD mimicking the externalization of peptides through the pores to the capsid exterior suggested that release of the first peptide is rate limiting, and that subsequent peptides are liberated more readily. Calculation of free energy profiles based on umbrella sampling confirmed that reduced pH lowers the barrier for peptide release.

3. Delivery and replication of genome

Following cell entry, the viral genome must be transported to the site of replication (Figure 1, step 2). The viral protein coat, or capsid, encasing the genome often plays a key role in this process. Central to the computational study of genome delivery is the development of models that describe the interplay of viral capsids with nucleic acid. Most all-atom simulations of genome-bound nucleocapsids have thus far focused on monomers or low-order oligomers, rather than biological assemblies [22, 23, 24, 25]. However, over the past fifteen years, atomistic simulations of intact capsids have become increasingly accessible [4, 26], providing an essential platform for examining their interactions with enclosed genome.

Importantly, the capsid must protect the genome throughout the process of delivery. The first all-atom simulations of an icosahedral nucleocapsid, that of satellite tobacco mosaic virus packed with RNA, revealed the key role of the genome in capsid structural integrity and dynamical stability [27]. The first all-atom simulations of a helical nucleocapsid assembly, that of the Ebola virus with spooled RNA, similarly indicated the stabilizing influence of genome,

and revealed the specific protein-protein and protein-RNA interactions that sustain the assembly [28]. A coarse-grain model of the novel coronavirus (SARS-CoV-2) nucleocapsid, also helical in architecture, likewise captured the spiraling complex with RNA [29].

Directed movement of the nucleocapsid through the cytoplasm requires recruitment of the host cell transport machinery. Atomistic MD of the hepatitis B virus (HBV) capsid noted significant translocation of sodium ions through its trimeric pores, suggesting these as portals for display of positively-charged peptides involved in transport signaling [30]. More recent all-atom simulation work revealed the interaction of the HIV-1 capsid with FEZ1, an adaptor protein required for interfacing the capsid with cytoskeletal motors for trafficking the genome to the nucleus [31]. Molecular details of the complex were used to construct the first full-scale model of capsid transport along microtubles by kinesin-1 (presented in [6]).

At just the right place and time, the viral genome must be released from the capsid, or otherwise rendered accessible to the replication machinery via the process of uncoating. Simulations of an RNA-packed picornavirus nucleocapsid using a phenomenological coarse-grain model suggested that uncoating proceeds via expulsion of up to three capsid pentamers, expected in response to acid-induced conformational change of the genome [32]. The resulting opening in the shell allowed RNA to exit without uncoiling of double-stranded segments. A simliar study applied to RNA-packed iflaviruses suggested that, in response to genome expansion at low pH, the capsids of some members of the virus family crack open and fragment, while others swell and open like "flowers." Both uncoating mechanisms enabled rapid release of the genome for delivery into the cytoplasm [33]. Additional coarse-grain work introduced a negative charge imbalance into an empty Triatoma virus, mimicking the presence of RNA after leaking of protons to the capsid exterior in response to acidification [34]. The resulting internal pressure forced the capsid to crack open, providing a qualitative representation of uncoating. Recently, disassembly of the empty HBV capsid was investigated using atomistic simulations, applying an external force to pull the capsid apart and allowing speculation on its uncoating mechanism [35].

Viral capsids sometimes serve as metabolic containers for reverse transcription, in which packaged RNA is transcribed to DNA prior to genome release. All-atom simulations of the intact HIV-1 capsid revealed the translocation of chloride ions through hexagonal pores, suggesting these may also be an entryway for negatively-charged metabolites, such as the nucleotide building blocks required for DNA synthesis [36]. By combining replica exchange MD with umbrella sampling, the permeation of nucleotides into the capsid was examined [37]. Free energy profiles indicated that transport of a single nucleotide is unlikely, but co-transport with a second nucleotide or the host factor inositol hexakisphosphate (IP6) reduced the barrier to entry, supporting a cooperative transport mechanism fueling reverse transcription. Atomistic simulations have also been applied to investigate the pentagonal pores of the insect-born Omono River virus, suggesting that anions stabilize closed conformations of the pore, which must open to facilitate nucleotide import [38].

Owing primarily to their value as drug targets, viral genome synthesis machinery has also been investigated with computational methods. The reverse transcriptase of HIV-1 has been widely studied at atomistic resolution, as well as with quantum mechanics calculations, with focus on its selectivity and enzymatic mechanism [39, 40, 41] and inhibition by non-nucleoside reverse transcription inhibitors (NNRTIs) [42, 43]. The dengue virus nonstructural protein 3 (NS3), a key component of the flavivirus replication complex, was likewise examined with respect to its interaction with genome. NS3 is responsible for ATP-dependent unwinding of dsRNA, and all-atom simulations examined the enzyme in each of its distinct substrate states, revealing the basis for allosteric enhancement of hydrolysis by bound RNA [44].

4. Assembly and maturation of progeny

Following replication, viral progeny assemble, either in the cytoplasm, within a specific organelle, or at the plasma membrane of the cell surface, depending on the virus (Figure 1, step 3). A key aspect of assembly is encapsidation of the genome. Coarse-grain modeling has played a significant role in investigating the self-assembly of viral capsids and the process of genome packaging [45], particularly with respect to icosahedral capsids forming around strands of RNA. For example, particle-based simulations of the simian vacuolating virus 40 capsid with RNA examined the dependence of its assembly pathway on ionic strength and the balance between protein-protein and protein-genome interactions [46]. Monte Carlo sampling assessed self-assembly of generalized capsid subunits, revealing spontaneous shell curvature and preferential formation of symmetric structures [47]. Using a similar generalized model, transition from disordered assembly intermediates into ordered, icosahedral capsids was shown to exploit the intrinsic elasticity of the growing capsid and preserve icosahedral order across distinct assembly pathways [48].

HBV is a well-established model system for the experimental study of capsid assembly. Atomistic simulations of capsid protein dimers and early assembly intermediates have explored the effects of amino acid substitutions [49] and small-molecules [50, 51, 52, 53, 54], relating induced structural changes to altered HBV assembly kinetics and product morphologies. Intact HBV capsid simulations revealed the structural basis for enhanced assembly and increased drug resistance in mutants [55] and suggested new insights into the conformational and allosteric regulation of assembly [26]. Unconstrained MD demonstrated that the icosahedral capsid can adopt faceted geometries to accommodate the binding of assembly-accelerating compounds [56] or break symmetry to accommodate genome maturation [30].

Rather than forming around the genome to enclose it, some viral capsids pre-assemble and import their genomes via a packaging motor incorporated at an icosahedral vertex. Several coarse-grain simulation studies have investigated general features of motor function and interactions with genome [57, 58]. Recent atomistic work on a bacteriophage packaging motor leveraged atomistic simulations of its distinct nucleotide states to investigate the relationship between hydrolysis and motor action [59]. ATP binding was correlated with high affinity for dsDNA, and observed conformational changes supported a helical-to-planar mechanism by which the motor generates force to translocate dsDNA. Another study identified a glutamate switch involved in the transference of the ATP-binding signal, revealing further details of the motor mechanism [60].

Some viruses are translated into polyproteins that are subsequently cleaved and re-assembled to produce the mature virus. All-atom simulations of the SARS-CoV-2 main protease, which carries out such polyprotein processing, characterized the effect of mutations on hydrolysis activity [61], showed that the active site of the protease homodimer is more accessible and has a higher affinity for the polyprotein substrate than protease monomers [62], and revealed a mechanism of inhibition that prevents polyprotein cleavage and arrests viral maturation [63]. Similarly, computational studies of the HIV-1 protease applied enhanced-sampling simulations and mixed quantum mechanics/molecular mechanics calculations to uncover details of its substrate binding pathway and hydrolysis mechanism [64, 65, 66, 67].

The HIV-1 polyprotein, known as Gag, assembles at the cell plasma membrane to form an immature particle. Integrative atomistic and multi-scale endeavors examined the architecture and stability of the polyprotein lattice of HIV-1 and other retroviruses [68, 69, 70, 71]. All-atom MD studies indicated that the cellular host factor IP6 promotes formation of the HIV-1 Gag lattice and, later, the mature HIV-1 capsid by stabilizing hexameric oligomers [72, 71]. Atomistic simulations with simulated tempering invested a key HIV-1 maturation intermediate, consisting of the capsid protein/SP1 peptide [73]. Results showed that the SP1 six-helix bundle undergoes helix-coil transitions and that these dynamics are essential to continued proteolytic processing. The final step of HIV-1 maturation, assembly of the mature capsid around the viral RNA, was investigated with a growing elastic sheet model that mimicked the progressive addition of protein subunits [74]. This physics-based simulation work suggested that sufficiently large sheets curl over on themselves to facilitate formation of the conical capsid, providing an explanation for experimentally-observed capsid mythologies.

5. Release from the host cell

Egress of enveloped virions from the host typically involves budding from the cell surface or fusion of the intracellular transport vesicle with the cell plasma membrane for particles assembled and budded elsewhere (Figure 1a, step 4). Non-enveloped viruses may exit via cell lysis or a process of non-lytic export (Figure 1b, step 4). During budding, the former acquire their envelopes, or membraneous outer layers embedded with glycoprotein receptors, viroporins, or other key antigens important for host escape and the next cycle of cell entry. Shape-based coarse-grain simulations of the Sindbis virus glycoproteins and nucleocapsid local to a model plasma membrane supported a nucleocapsid-directed budding mechanism [75]. Another study of the budding HIV-1 envelope with glycoproteins at similar resolution investigated their role in induced membrane curvature and budding kinetics of the immature virion [76]. Shape-based coarse-grain simulations also showed that the influenza A M2 viroporin clustered in the host membrane under conditions that mimic the environment just prior to viral budding, serving to stabilize the system and lower the free energy, favoring particle formation [77].

Influenza A neuraminidase (NA), already widely investigated with all-atom computational work [4], plays an essential role in escape of budded progeny via cleaving the host receptor glycans recognized for cell re-entry by its counterpart HA. Atomistic studies examining NA showed that variable substrate specificity across different influenza A strains contributes to viral pathogenesis [78] and that stalk-deletion mutants increase virulence by altering the geometry of the substrate binding pocket [79]. All-atom simulations of four replicate influenza A virus-like particles (VLPs) corresponding to strains of swine, avian, and lab-created origin revealed that NA activity with the substrate

was higher than that of HA, despite HA being nearly eight times more common on the VLP surface [80]. Further analysis indicated reduced membrane curvature associated with clusters of NA, increasing the available surface area for receptor recognition. These observations provide important mechanistic explanations for the functional balance between HA and NA surface proteins, key to the influenza A life cycle.

6. The extracellar virion

Following release from the host cell, the virus exists as an extracellular entity called a virion (Figure 1, step 5). The virion is a self-contained infectious particle that includes the packaged genome and everything the virus needs to infiltrate a new host and repeat the viral life cycle. Enabled by high-performance supercomputing, as well as the availability of higher-resolution structural data describing larger and more complex viral assemblies, recent efforts in the field of computational virology have focused on integrative modeling and simulation of entire virions. While the only atomistic and architecturally complete model virions produced to date describe simple plant and insect viruses composed solely of capsid and genome [27, 81, 82], important progress has been made in developing models of enveloped viruses of key relevance to human health, particularly those responsible for recent epidemics and pandemics.

A coarse-grain model representing the outer shell of the influenza A virion included a 74-nm envelope displaying membrane-embedded HA, NA, and M2 viroporin proteins [83]. Similarly, a coarse-grain model of the dengue virion was based on a 50-nm particle encompassing the envelope and its outer protein shell, formed by membrane-embedded, interlocking E and M proteins [84]. Both simulations explored the effects of heterogeneous lipid compositions on envelope biophysics and diffusion of the constituent proteins. A muti-scale model of the Zika virion, analogous in architecture to that of dengue, was developed as a test case for the optimization of software for building and simulating large membrane-based biomolecular systems [85].

A coarse-grain model representing the inner layer of the immature HIV-1 particle, which matures to an infectious virion only after cellular export, included the Gag polyprotein lattice within a 125-nm lipid envelope [86]. Following equilibration in the context of this assembly, an isolated hexamer of CA domains, which go on to form the capsid following cleavage of Gag, was investigated with atomistic simulations to establish key interactions responsible for maintaining hexagonal symmetry in the lattice. Another coarse-grain study focused solely on the HIV-1 envelope, in the absence of embedded proteins, modeled as a 150-nm liposome with authentic biological lipid composition [87]. Characterization of its biophysical properties revealed new insights into lateral and transverse diffusion, as well as the envelope's asymmetry, flexibility, and heterogeneous dynamics–all of which provide an important basis for future work exploring the processes of viral membrane fusion and budding. Following equilibration, the complete coarse-grain liposome was backmapped to produce an atomistic model, requiring a top-ten supercomputer to handle interactions between 280 million constituent atoms [88].

An atomistic model describing the exterior of the intact influenza A virion, including unglycosylated HA and NA, was also developed, spanning 115 nm and encompassing 160 million atoms [89]. Combining sampling from many copies of NA, which is involved in escape of progeny virions from the cell surface, enabled examination of substrate recognition and the role of a secondary receptor binding site. Finally, a coarse-grain model of the SARS-CoV-2 virion was realized [29], including a 100-nm envelope with membrane-embedded S, M, and E proteins. Construction of the model is ongoing, and aims to include the nucleocapsid, composed of the helical N protein complexed with RNA. A multi-scale model of the SARS-CoV-2 virion, derived in a parallel collaborative effort by the authors and likewise under continued development, is shown in Figure 2.

7. Prospects

Characterizing molecular motion and the dynamics of viral life cycle processes is fundamental to establishing the determinants of infection, as well as devising novel strategies for its treatment and prevention. MD simulations are being widely applied to study viruses, complementing experimental investigations to reveal important insights into viral biology and its inhibition. While the main focus of MD has been equilibrium simulations of isolated components of virus structures, progress in computational methodologies and supercomputing power are driving a shift in the field of computational virology toward the construction of larger, more comprehensive, and increasingly realistic models, as well as the application of advanced simulation techniques that mimic the dynamics of active life cycle processes, even at atomic resolution. Further, the progressive availability of higher-resolution experimental structures of complex viral assemblies, obtained within more physiologically-representative conditions, including *in situ* [90], are accelerating the

development of more holistic and accurate integrative models, along with computational studies designed to examine the infection processes they carry out. Advances in data-guided simulation approaches are combining with heightened experimental capabilities to refine structural characterization even of historically well-studied systems [91]. Deeper examination of the physics underlying viral dynamics [92] benefits the tuning of accurate simulations designed to examine virus function.

While the protein components of viral systems remain the best characterized, recent years have seen increased consideration of post-translational modifications, including glycosylation. Future progress toward producing realistic models and model processes relevant to the study of viruses will require more and higher-quality structural data describing authentic viral genomes and their encapsidated conformations, as well as the aggregation of data characterizing the compositions and biophysics of complex viral lipidomes. Beyond investigation of virus attachment and assembly, seeking leads to inhibit entry and particle reproduction, more computational study of intracellular trafficking is warranted, capturing details of transport to the site of replication and egress that may be exploited for drug targeting.

Finally, the escalation toward more extensive and computationally expensive models and simulations necessitates the development of new strategies for approaching large-scale calculations, including leveraging judicious multi-scale strategies [6] and taking advantage of emerging technologies like artificial intelligence [93]. Further, larger models and simulations will produce yet larger datasets that must be efficiently processed. High-performance analysis tools must be developed that are capable of handling both model complexity and data footprint [94, 95] to extract meaning and render such large-scale computational endeavors worthwhile. Constructing and simulating models of viruses is only the beginning; interrogating the resulting structures and trajectories to make scientific discoveries is paramount. Integrative computational methods, when closely guided by experiments, are unmatched in their potential to reveal the details of viral life cycle dynamics needed to drive the development of new interventions to thwart viral infection.

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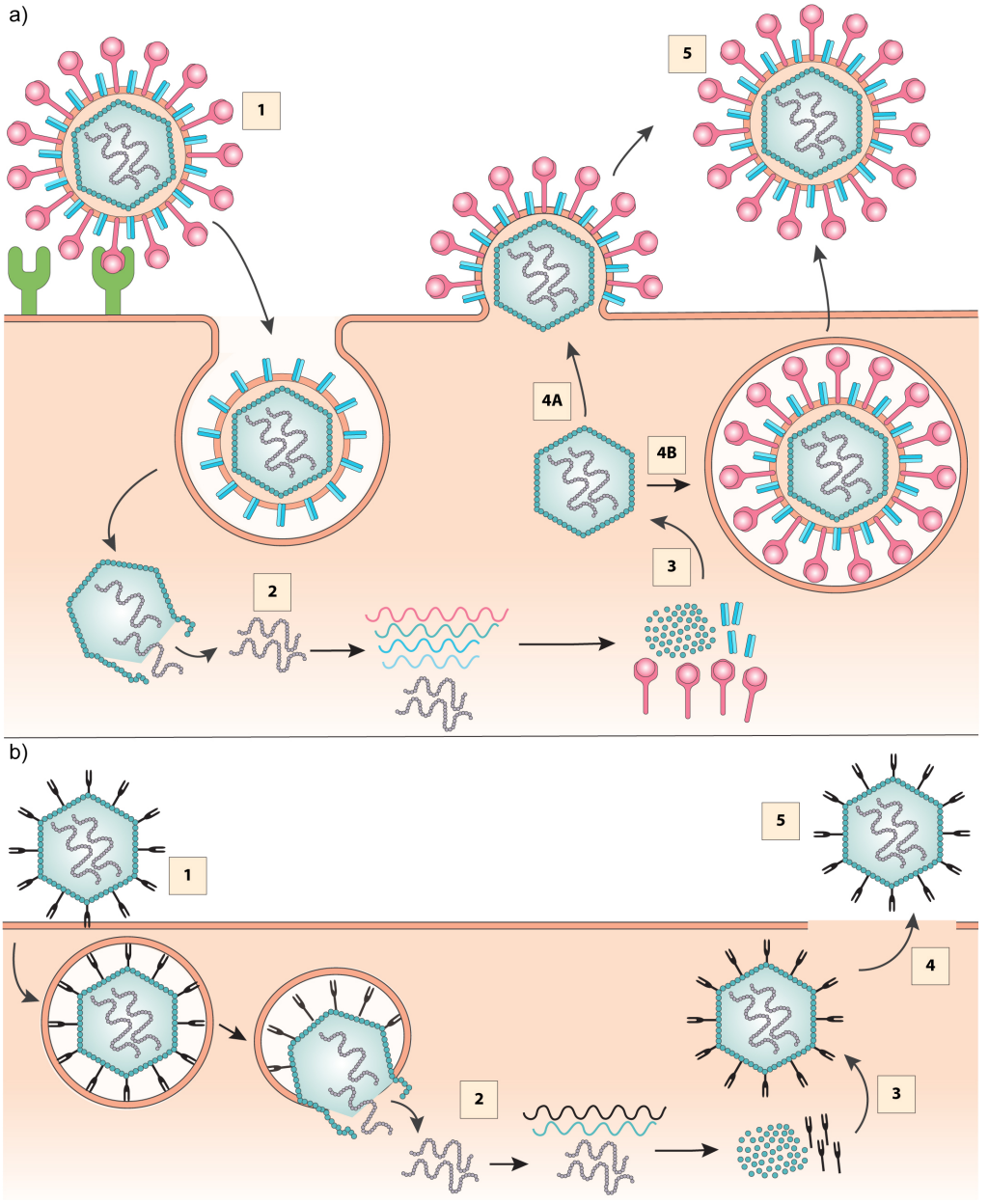

Figure 1: The viral life cycle comprises a complex sequence of processes that is unique to each virus-host system, but generally includes five stages: (1) Host cell attachment and entry, (2) Delivery and replication of genome, (3) Assembly and maturation of progeny, (4) Release from host cell, (5) Extracellular virion seeking new host. Following recognition of host cell receptors, many viruses infiltrate the cell via the endocytotic pathway (step 1). To complete entry, enveloped viruses may fuse membranes with that of the endosome (**panel A**, e.g., influenza A), while non-enveloped viruses may lyse the endosomal membrane (**panel B**, e.g., FHV). Following replication (step 2), new viral particles assemble (step 3). Assembly may occur in the cytoplasm (e.g., HBV), within a specific organelle (e.g., SARS-CoV-2), or at the cell surface (e.g., HIV-1). Enveloped viruses may gain their protein-studded envelopes via budding and releasing directly from the plasma membrane (**panel A**, step 4A), or via budding from the organelle where they assembled (**panel A**, step 4B) and trafficking to the cell surface for release. Non-enveloped viruses may employ cell lysis as their means of egress (**panel B**, step 4). Depending on the virus, maturation may occur before (e.g., HBV) or after (e.g., HIV-1) release from the host.

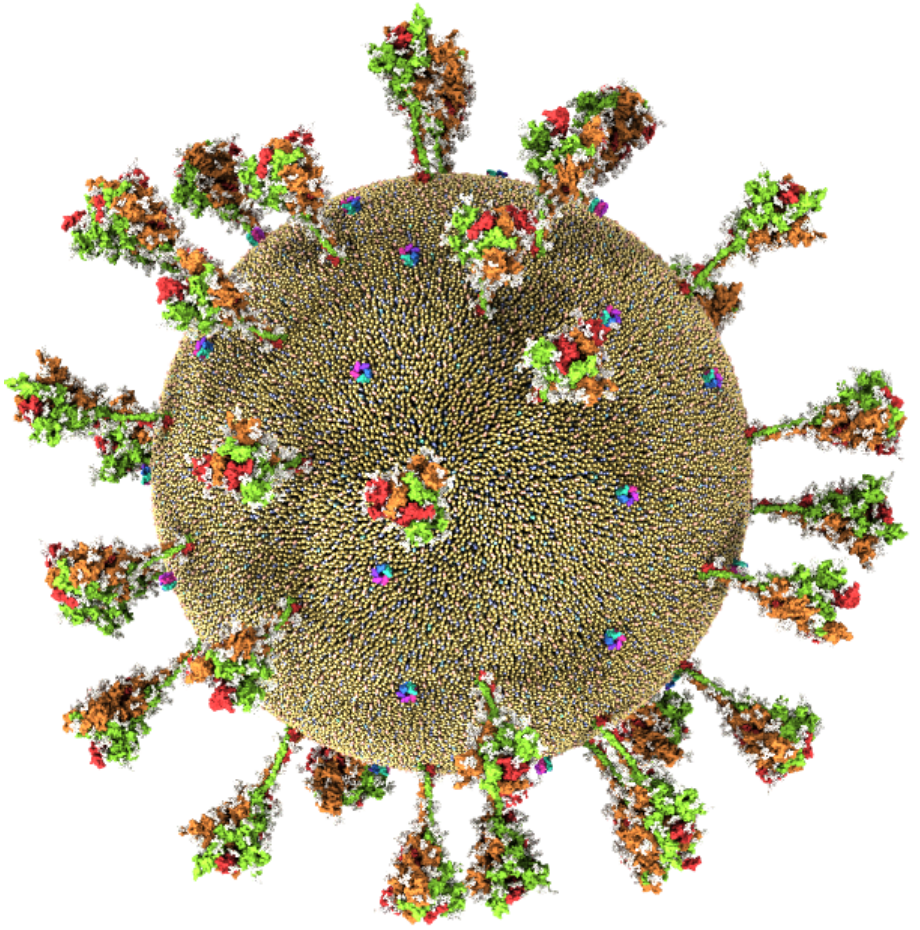

Figure 2: Multi-scale model of the SARS-CoV-2 extracellular virion. The enveloped SARS-CoV-2 virion is decorated with characteristic glycoprotein spikes that confer the appearance of a "corona." The model was produced by integrating structural, biochemical, and biophysical data obtained from experiments with computational modeling and large-scale MD simulations.