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Review

Application of Molecular Dynamics Simulations in Vaccine Design for Arboviruses

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How To Cite: Chao, D.-Y. Application of Molecular Dynamics Simulations in Vaccine Design for Arboviruses. *eMicrobe* **2026**, *2*(4), 19. https://doi.org/10.53941/emicrobe.2026.100019

Received: 26 August 2026
Revised: 2 November 2026
Accepted: 4 November 2026
Published: 12 November 2026

Abstract: Arboviruses, which comprise three virus families, are a diverse group of viruses transmitted by insects. While most arboviral diseases remain zoonotic and persist in a sylvatic cycle, some viruses, such as dengue (DENV) and chikungunya (CHIKV), have adapted to an urban cycle, with humans as the primary amplification host, causing significant medical consequences. While the live-attenuated (LA) vaccine against yellow fever virus has proven successful in providing protective immunity, safety concerns about other LA vaccines against DENV and CHIKV remain. Enveloped virus-like particles (eVLPs) have emerged as a leading vaccine platform for arboviruses, including dengue, Zika, and chikungunya, because they recapitulate the antigenic surface of authentic virions without infectious risk. Yet most eVLPs lack solved structures, and the interaction between the envelope protein and the lipid bilayers remains unknown, leaving key questions about assembly, stability, and immunogenicity unresolved. This review examines how molecular dynamics (MD) simulations, spanning all-atom and coarse-grained resolutions and increasingly deployed in multiscale workflows, are being integrated with cryo-electron microscopy to address these gaps. Structural comparisons show that flavivirus eVLPs typically adopt T = 1 icosahedral symmetry built from the same asymmetric prM-E trimer that organizes T = 3 virions. MD studies of dengue eVLPs reveal how E-M protein clusters act as membrane-bending units, and how in silico mutagenesis of lipid-facing residues can be translated into experimentally validated, secretion-enhancing eVLP variants. MD simulation has matured from a descriptive tool into an active driver of rational eVLP engineering, and its continued integration with cryo-EM, AI-accelerated force fields, and enhanced sampling methods will be essential for next-generation arbovirus vaccine design.

Keywords: molecular dynamics; simulation; enveloped virus-like particles; lipid bilayer; lipid composition; structure

1. Introduction

Arthropod-borne viruses (Arboviruses) represent a diverse group of pathogens transmitted to susceptible vertebrate hosts by hematophagous arthropods such as mosquitoes, ticks, sand flies, and biting midges [1]. These viruses generally undergo an extrinsic incubation period within the vector, multiplying in the midgut and spreading to the salivary glands before being injected into a host during blood feeding. While most arboviral diseases are zoonoses maintained in a sylvatic cycle between vectors and wild animals, some viruses, such as dengue (DENV)

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and chikungunya (CHIKV), have adapted to an urban cycle in which humans serve as the primary amplification host [2]. Among them, DENV is the most important arboviral pathogen, with an estimated 390 million dengue virus infections occurring worldwide each year, of which approximately 96 million demonstrate various clinical manifestations from mild symptoms to severe hemorrhage [3]. Because arboviruses overlap geographically, the disease burden at the country or regional level was usually underestimated [4–6]. Although urban cycle-adapted arboviruses pose a major human health challenge today, the emerging zoonotic potential of other arboviruses, such as Zika virus (ZIKV), Usutu virus (USUV), or Oropouche virus (OROV), is increasingly threatening public health [7–9].

Most arboviruses causing human disease belong to three primary groups: *Flaviviridae* (genus Flavivirus), *Togaviridae* (genus Alphavirus), and the order *Bunyavirales* [1]. All three arbovirus groups are enveloped viruses. Central to the biology of all enveloped viruses is the lipid bilayer envelope acquired from host cell membranes during the assembly and budding process. Their life cycles—encompassing host cell attachment, membrane fusion, intracellular replication, and particle egress—are governed by complex, transient molecular interactions among viral proteins, lipid membranes, and host factors [10]. This envelope is not merely a passive structural shell: its specific lipid composition, asymmetry, curvature, and protein content are actively regulated and critically determine viral infectivity, immune evasion, membrane fusion, and vaccine antigenicity [11,12]. Understanding these interactions at the molecular level is critical for rationally designing vaccines, therapeutics, and prophylactic strategies.

Enveloped virus-like particles (eVLPs) have emerged as a promising platform in the field of vaccine development due to their ability to mimic the structure and immunogenicity of actual viruses. Historically, the concept of using virus-like particles for immunization can be traced back to early vaccine methodologies, where researchers sought to leverage the inherent immunogenic properties of viral components without the associated risks of live pathogens [13]. These particles present viral antigens in a manner that closely resembles natural infection, thus eliciting robust immune responses. The importance of eVLPs has been underscored by their applications against various viral pathogens, particularly in the context of global health challenges posed by arboviruses.

The unique ability of eVLPs to present multifaceted antigenic profiles has enabled enhanced immune recognition, which is crucial for generating both humoral and cellular immunity [14,15]. In particular, the successful demonstration of engineering eVLPs to reduce antibody-dependent enhancement in preclinical models has paved the way for their use in human vaccines, as evidenced by ongoing clinical trials focused on dengue virus (DENV) and chikungunya virus (CHIKV) [16]. The evolution of eVLP technology has been fueled by advances in genetic engineering and expression systems, notably the utilization of insect or Drosophila cell lines for eVLP production [14]. This approach not only improves the quality of the glycoproteins expressed on eVLPs but also enhances the scalability and safety of vaccine production, a critical factor in pandemic response scenarios. While these innovative platforms promise to produce eVLPs, most eVLPs lack available structures, and their envelope proteins are decorated with glycans derived from insect cells rather than mammalian sources. As emerging infectious diseases continue to pose challenges, exploring eVLPs as a versatile vaccine platform remains highly promising. This review focuses on recent advances in integrating protein structure and molecular dynamics (MD) simulations to improve eVLP stability and immunogenicity. The goal is to address mechanistic questions and direct mutant selections using simulated results with clear implications for engineering and producing eVLPs. To achieve this goal, we excluded studies that relied on in silico simulations without experimental validation.

2. Icosahedral Symmetry as the Dominant Organizing Principle of eVLP and virion

Flavivirus virions (dengue, West Nile, Zika) adopt T = 3 icosahedral symmetry with 180 copies each of the envelope (E) protein and membrane protein precursor (prM), arranged as 60 asymmetric trimeric prM–E spikes in the immature form [17]. Upon furin cleavage and pr peptide release, the 180 E subunits reorganize into 90 flat E dimers in the mature form, grouped into 30 “rafts” of three parallel dimers [10]. In contrast, all dengue VLPs studied, both the mature mD2VLPs and the immature imD2VLPs, adopt T = 1 symmetry with only 20 trimeric prM–E spikes (60 copies of E) in the immature form [18], or 30 E dimers in the mature form [19]. This size reduction reflects the absence of a nucleocapsid core to template the larger T = 3 lattice, confirming that the nucleocapsid core determines virion geometry. The immature T = 1 VLP surface described by Palur et al. [18] is strikingly similar to a scaled-down version of the immature T = 3 virion surface, with the same protomeric spike unit (asymmetric trimer of prM–E heterodimers) arrayed on a smaller scaffold.

The exception within the flavivirus VLP corpus is the small VLPs (smVLPs) described by Johnson et al. [20]. Their cryo-EM structure revealed octahedral rather than icosahedral symmetry: 24 asymmetric trimers of prM–E heterodimers (72 copies each of prM and E) arranged on an octahedral surface lattice. This is the same protomeric unit as in icosahedral immature virions and T = 1 VLPs, an asymmetric trimer, but assembled on a fundamentally different geometric scaffold. The octahedral shell accommodates a lower copy number of the prM–

E trimer than the T = 1 icosahedral shell (24 vs. 60 copies of E), producing a smaller particle. This unexpected symmetry shows that the prM–E trimer can tile multiple closed geometries, with the outcome depending on stochastic particle-assembly kinetics in the absence of a nucleocapsid template.

Alphavirus virions universally adopt T = 4 icosahedral symmetry with 240 copies each of E1 and E2 (with E3/6K transient peptides), organized as 80 trimeric spikes. Both the chikungunya VLPs described by Urakami et al. [21] and those used as immunogens in Raju et al. [22] faithfully recapitulate this T = 4 organization. Urakami et al. further showed that expressing only the structural proteins in their uncleaved, "immature" conformation—retaining E3 on the spike surface—produces VLPs with a visibly spikier surface that enhanced immunogenicity compared with the smooth mature form, suggesting that spike geometry itself modulates the adjuvant effect. The lenticular cross-section and radial organization of the alphavirus T = 4 lattice is structurally distinct from the flatter, raft-organized flavivirus T = 3/T = 1 surface, yet both are icosahedrally symmetric—a reflection of the independent evolutionary solutions to enveloped virus assembly.

3. Molecular Dynamics (MD) Simulations

Molecular dynamics (MD) simulations have emerged as an indispensable tool for investigating eVLP and lipid interactions at atomic or coarse-grained resolution [23]. Traditional experimental techniques such as X-ray crystallography, cryo-electron microscopy (cryo-EM), and nuclear magnetic resonance (NMR) spectroscopy have provided extraordinary structural snapshots of viral proteins and assemblies. However, these methods capture predominantly static or time-averaged structures and provide limited information about the dynamic processes, i.e., conformational changes, lipid rearrangements, protein-membrane binding, that govern viral biology. This is precisely the gap that computational simulation, and in particular molecular dynamics (MD) simulation, has proven uniquely suited to address [24,25]. By providing access to time and length scales complementary to experimental structural methods, MD simulations reveal the dynamic molecular basis of lipid–protein interactions, membrane curvature induction, matrix protein oligomerization, and glycoprotein conformational dynamics that are difficult or impossible to access by experiment alone.

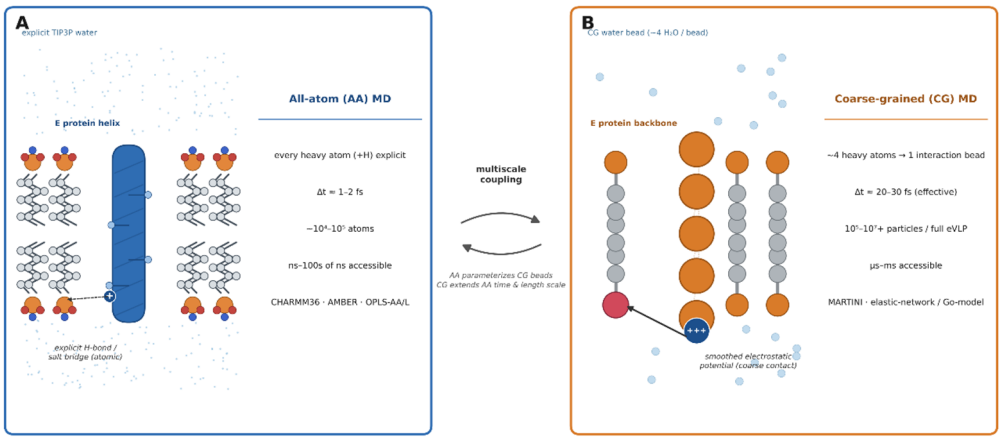
MD simulations treat atoms and molecules as classical particles governed by Newton's equations of motion, integrating these equations over time to generate trajectories that describe the evolution of a molecular system. The method models a system of N atoms, each described by its position $r_i(t)$ and velocity $v_i(t)$, evolving according to Newton's second law of motion:

$$F_i = m_i \times a_i = -\nabla_i U(r_1, r_2, ..., r_N)$$

where F_i is the force on atom i, m_i its mass, a_i its acceleration, and U the potential energy function—also called the force field—that depends on the positions of all atoms in the system. The equations of motion are integrated numerically using algorithms such as the Verlet, velocity-Verlet, or leapfrog integrators with timesteps typically between 1 and 2 femtoseconds for all-atom simulations.

The potential energy function (force field) encodes all interatomic interactions: covalent bonds (bond stretching, angle bending, dihedral torsions), and non-bonded interactions (van der Waals forces described by Lennard-Jones potentials, and electrostatic interactions described by Coulomb's law). In biomolecular simulations, long-range electrostatic interactions are typically handled using the Particle Mesh Ewald (PME) method, which efficiently calculates electrostatic forces in periodic boundary condition (PBC) systems. The choice of force field critically determines simulation accuracy; major force fields used in virion or VLP structural studies include CHARMM36, AMBER12:EHT, OPLS-AA/L, and MARTINI (for coarse-grained systems).

All-atom (AA) MD simulations represent every non-hydrogen atom (or include hydrogen, depending on the force field) explicitly. This level of detail enables high-fidelity capture of fine-grained molecular interactions—specific hydrogen bonds, salt bridges, hydrophobic contacts, and water-mediated interactions. AA-MD is particularly valuable for studying specific mutations, antigen–antibody recognition, protonation, glycan contacts, or local interactions affecting particle stability. While AA-MD provides atomic resolution, it is computationally expensive, typically limiting simulations to systems of tens to hundreds of thousands of atoms and timescales of hundreds of nanoseconds. Many biologically relevant phenomena in virology, such as lipid diffusion, protein clustering, membrane curvature, viral particle assembly, occur on microsecond timescales and require system sizes of millions of particles. Sufficient sampling, such as Martini, elastic-network models, and Go-like approaches with different assumptions about protein flexibility and interaction strengths, could overcome these challenges. Coarse-grained (CG) MD, by contrast, addresses this challenge by grouping multiple atoms into single interaction sites ("beads"), simplifying the energy landscape and dramatically increasing both simulation speed and accessible timescales (Figure 1).



Parameter	All-atom (AA) MD	Coarse-grained (CG) MD
Resolution	every non-hydrogen atom explicit (± H)	~4 heavy atoms grouped per interaction bead
Integration timestep	1–2 fs	20–30 fs (effective)
Accessible timescale	tens–hundreds of ns	microseconds–milliseconds
Typical system size	10^4–10^5 atoms (local patch)	10^5–10^7+ particles (full eVLP / vesicle)
Interaction detail	explicit H-bonds, salt bridges, waters	smoothed electrostatic / van der Waals potentials
Representative force fields	CHARMM36 · AMBER12:EHT · OPLS-AA/L	MARTINI · elastic-network / Go-like models
Best suited for (eVLP studies)	point mutations, antigen–antibody epitopes, specific lipid head-group contacts	membrane curvature, vesiculation, full-particle morphology & assembly

Figure 1. All-atom versus coarse-grained molecular dynamic (MD) simulation representations of envelope protein–lipid bilayer interaction. Both resolutions model the same embedded envelope protein–lipid interaction. (**A**) All-atom (AA) MD retains every heavy atom, resolving specific hydrogen bonds and salt bridges, but at high computational cost and over short accessible timescales. (**B**) Coarse-grained (CG) MD merges groups of atoms into single interaction beads (e.g., the MARTINI ~4:1 heavy-atom-to-bead mapping), trading atomic detail for access to the microsecond–millisecond, whole-particle scales needed to study eVLP membrane curvature and vesiculation. Multiscale workflows couple the two: AA simulations parameterize or validate local interactions that CG simulations then propagate across the full eVLP. The table below the panels summarizes the key differences between the two approaches in resolution, integration timestep, accessible timescale, typical system size, interaction detail, representative force fields, and the eVLP-study questions each is best suited to answer. The graph was generated with the assistance by artificial intelligence, Claude model sonnet 5.

A growing trend is the use of multiscale simulation strategies that combine AA and CG methods. A common workflow involves first performing AA-MD to capture atomic-resolution details of specific protein-lipid interactions or binding sites, then "coarse-graining" the resulting system to extend simulations to longer timescales and larger length scales. The dengue VLP study by Palur et al. exemplifies this approach: AA-MD first probed protein-lipid and protein-protein interactions at the E and M protein dimer interface, and CG simulations then reproduced full VLP morphologies that closely matched cryo-EM micrographs [18]. This multiscale strategy allows researchers to achieve both mechanistic detail and biological relevance within a single computational framework. This structure-guided MD approach has become a standard methodology for studying large viral assemblies where cryo-EM provides the global architecture, but MD reveals the dynamic molecular details, as shown in different virus systems, such as Ebola virus VLP40, HIV-1 matrix protein, and SARS-CoV-2 M and E proteins [26–28].

4. MD Simulation on eVLP of Dengue Virus

MD simulation is beginning to shift from simulating infectious particles to simulation-assisted antigen and VLP engineering, particularly in arbovirus research. Even fewer studies apply MD simulation to guide eVLP vaccine design with experimental validation. Soares et al. performed a pioneering CG-MD study of membrane vesiculation induced by dengue virus E and M proteins using GROMACS 4 and the CHARMM36c force field with TIP3P water [29]. Temperature was maintained at 310 K using the Berendsen algorithm. The work demonstrated that an arrangement of three E-M heterotetramers (denoted EM_3) constitutes a fundamental bending unit capable of generating positive membrane curvature. Computational modeling showed that an ordered cluster of five such bending units generates a closed vesicle in silico—directly reminiscent of the viral budding process. In silico mutagenesis of charged residues in the anchor helices of E proteins modulated vesicle formation,

establishing the structural determinants of dengue virus envelope-driven membrane curvature. This study provided one of the first molecular-level views of flavivirus budding energetics and geometry.

Palur et al. [30] combined AA-MD and CG-MD to guide structure-based mutagenesis of the dengue serotype 2 VLP. AA-MD probed protein-lipid and protein-protein interactions at the E protein helical region (E-H1), which sits near the lipid headgroups of the outer bilayer leaflet. In silico mutations of hydrophobic-facing residues (L398, F402, T405, A409, L412, L415) that point toward the lipid tails showed stronger protein-lipid interactions compared to wild-type, without disrupting surface epitopes. These computational predictions guided experimental site-directed mutagenesis, which confirmed substantially enhanced VLP secretion. Subsequent CG simulations of full dengue VLPs reproduced particle morphologies closely resembling cryo-EM micrographs, validating the multiscale computational approach as a reliable tool for VLP engineering.

In the most recent and ambitious dengue VLP study by Palur et al. [18], multiscale MD simulations were integrated with cryo-EM to characterize the maturation transition of dengue VLPs produced in CHO-K1 cells. CG simulations informed by measured lipid compositions (including diacylglycerol [DG] and phospholipid [PL] fractions from vesicle experiments) reproduced the lipid compositions of immature and mature VLP membranes. MD simulations demonstrated strong interactions between E proteins and anionic PS lipids in the mature VLP, contributing to particle stabilization, while in the immature particle these interactions were more dynamic. This tight integration of computational and experimental data represents a state-of-the-art multiscale approach to understanding VLP biology.

5. Lipid Bilayer of eVLP in MD Simulation

(1) Lipid specificity

A crucial part of all enveloped viruses is the lipid bilayer envelope acquired from host cell membranes during assembly and budding, and the exquisite specificity of envelope-lipid bilayer interactions depends on assembly or budding sites. Because orthoflaviviruses bud from the endoplasmic reticulum (ER) membrane, the eVLP was expected to have a similar lipid composition. MD simulations have been instrumental in delineating the molecular basis of this specificity, which is crucial because the viral budding site must be precisely defined within the complex lipid landscape of the host cell plasma membrane. While the lipid envelope of orthoflaviviruses is primarily composed of sphingolipids and glycerophospholipids, enriched in cholesterol and phosphatidylcholine (PC), the most abundant phospholipid, followed by phosphatidylserine (PS), the lipid composition of eVLP differed [30]. MD simulations showed that different lipid compositions lead to different interaction patterns [30].

Similar to Ebola VP40, the main matrix protein, which drives virus particle assembly and budding from the host cells, MD simulations showed that PI(4,5)P_2 and PS are the primary interaction partners for the matrix proteins, with the multiply charged PI(4,5)P_2 head group forming particularly strong and stable contacts with clusters of basic residues in the protein [31]. For Ebola VP40, PA lipids also appeared to play a role analogous to PS. The computational insights provided by MD simulation are fully consistent with experimental observations that depleting PI(4,5)P_2 or PS from the inner leaflet impairs Ebola VLP formation. Combined experimental and computational results provide crucial mechanistic details on how these lipids cluster around the protein and what the binding geometries are.

(2) Membrane curvature

Membrane remodeling is a fundamental requirement of viral budding, requiring the plasma membrane to curve away from the cytoplasm and eventually pinch off to release a new virion. MD simulations have contributed significantly to understanding how viral proteins induce and sense this curvature. The dengue envelope CG-MD study showed that E-M protein clusters act as geometric bending units, with specific curvature preferences determined by the amphipathic anchor helices [18,30,32]. It remains challenging to experimentally validate how curvature affects VLP assembly and budding. Also, the proposed VLP rearrangement by MD simulation may not be the only biological pathway. The dengue VLP engineering study used AA-MD to predict VLP-stabilizing mutations, which were then validated by site-directed mutagenesis showing enhanced VLP secretion [30]. The tight integration of MD predictions with experimental validation maximizes the value of both computational and experimental investments.

Similarly, the SARS-CoV-2 E protein MD study demonstrated that the pentameric E protein induces local lipid disordering and membrane curvature [33]. The palmitoylation study of influenza hemagglutinin demonstrated that lipid modifications of viral glycoproteins also contribute to membrane curvature at sites of viral budding [34]. The enveloped viruses exploit multiple distinct strategies—matrix protein oligomerization, transmembrane helix geometry, amphipathic helix insertion, and lipid post-translational modifications—to mechanically deform the host membrane during egress. This iterative computational-experimental cycle represents the most productive

application of MD in virology and is increasingly the standard of practice in the field. As VLP-based vaccines continue to gain regulatory approvals (e.g., HPV and HBV VLP vaccines, the SARS-CoV-2 VLP vaccine candidates), the role of MD simulation in rational VLP engineering of arboviruses will only grow.

6. Future Directions

The field of MD simulation in virology is evolving rapidly on multiple fronts. First, the development of AI-accelerated MD, including neural network interatomic potentials and machine learning force fields, promises to dramatically increase both accuracy and computational efficiency, potentially enabling routine all-atom simulations of complete viral particles [35]. Second, enhanced sampling methods such as metadynamics, replica exchange MD, and Gaussian accelerated MD are increasingly being applied to overcome timescale limitations and characterize rare conformational events such as membrane fusion intermediates [36]. Third, the integration of MD with cryo-EM and cryo-ET will continue to deepen, with the fitting of MD trajectories to EM density maps becoming a standard tool for structural refinement of complex viral assemblies. Fourth, the application of MD to antiviral drug discovery will expand, building on the examples of dengue NS1 inhibitor screening and SARS-CoV-2 E protein drug docking reviewed here, to encompass larger-scale virtual screening campaigns guided by MD-derived ensemble models rather than single static structures [37,38]. Finally, the engineering of next-generation VLP vaccines and biomimetic drug delivery systems will increasingly rely on MD simulation as a primary design tool, reducing the need for expensive and time-consuming trial-and-error experimental optimization.

7. Conclusions

Molecular dynamics simulation has matured into an essential tool in virology, providing molecular-level insights into viral protein-membrane interactions, assembly mechanisms, glycoprotein dynamics, and therapeutic targeting that are simply not accessible by experimental methods alone. The field has moved beyond proof-of-concept to become a routine component of virology research programs, with MD simulations routinely informing experimental design, explaining unexpected phenotypes, and guiding vaccine and drug development. As MD simulations can reveal unexpected long-range allosteric communication networks in viral glycoproteins [39], which would be entirely invisible in static crystal structures or cryo-EM, the ensemble approach by integrating MD and cryo-EM classification, cryo-electron tomography, NMR, HDX-MS, spectroscopy, and single-molecule experiments will provide the most convincing results for vaccine development (Figure 2).

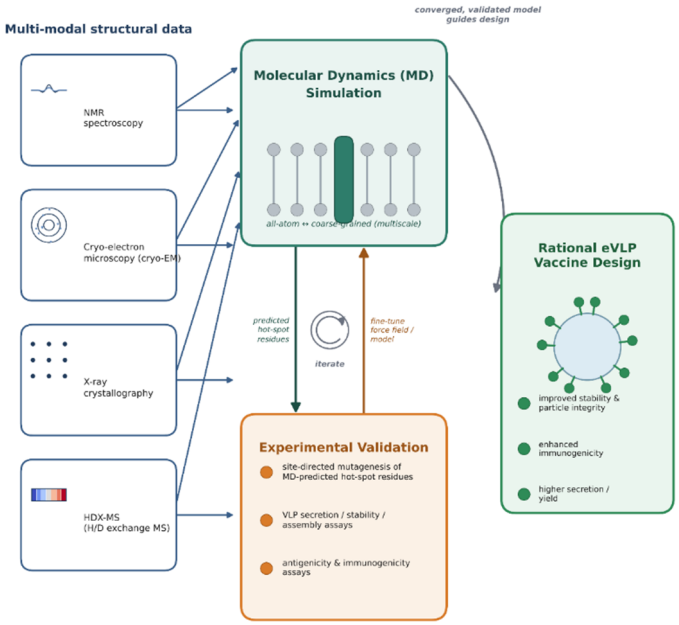


Figure 2. The emsembled approach to facilitate the eVLP (enveloped virus-like particles) production pipeline. Structural-data of viral envelope or eVLP from NMR, cryo-EM, X-ray crystallography or HDX-MS was feeded into MD simulation, which generates candidate hot-spot residues for site-directed mutagenesis and functional assays (Experimental Validation), whose results fine-tune the force field/model—closing an iterative design–build–test–learn loop—until the converged model guides rational eVLP vaccine design (improved stability, immunogenicity, yield). The graph was generated with the assistance by artificial intelligence, Claude model sonnet 5.

Funding

This research was funded by National Science and Technology Council (NSTC) grant number 114-2313-B-005 -045 and The APC was funded by NSTC.

Acknowledgments

I am sincerely thankful to Jan K. Marzinek from the Bioinformatics Institute (BII), Agency for Science, Technology and Research (A*STAR), Singapore, for his insightful comments on this review.

Conflicts of Interest

The author declares no conflict of interest.

Use of AI and AI-Assisted Technologies

During the preparation of this work, the author used Claude model sonnet 5 for the assistance to generate two figures. After using this tool, the author reviewed and edited the content as needed and takes full responsibility for the content of the published article.

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