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Original Article

Comparative Structural and Biophysical Profiling of Dengue Virus NS5 Methyltransferase Identifies DENV-4 as a Prioritized Antiviral Target

Afaf Salim Alwabli*, Ghadeer Fareed Bukhari

Department of Biological Sciences, Rabigh College of Science and Arts, King Abdulaziz University, Jeddah 21589, SAUDI ARABIA.

ABSTRACT

Background: The NS5 Methyltransferase (MTase) domain is essential for the capping and replication of dengue virus RNA and for the virus's evasion of the host immune response, making it a promising antiviral target. **Objectives:** To assess the structural and biophysical characteristics of the NS5 MTase across the four Dengue Virus Serotypes (DENV-1-4) and to identify features relevant to antiviral and antibody design. **Materials and Methods:** An *in silico* comparative study was performed, incorporating sequence mapping, Fab-interface modelling, electrostatic and hydrophobicity profiling, developability prediction using Poly-Specificity Reagent (PSR)-like metrics, and electrostatic-stability prediction across a range of pH and ionic-strength conditions. **Results:** The NS5 MTase was highly conserved among serotypes, with a few substitutions at the predicted Fab-binding interfaces. The dominant contact residues were Pro114 (DENV-1/4), Tyr88 (DENV-2) and Ile49 (DENV-3). Surface electrostatic features were largely conserved, with slight hydrophobic variation. Among the developability descriptors examined, DENV-4 separated most clearly from the reference distribution in the PSR-like space, consistent with a favourable predicted non-specificity profile. Maximum electrostatic stability for all serotypes occurred at pH 6.0-8.0 and low ionic strength (≤0.05 M), and the energy landscape within this window was flattest for DENV-4. **Conclusion:** Despite the high conservation of the NS5 MTase, serotype-specific structural differences may influence its therapeutic targeting. DENV-4 demonstrated the most favourable predicted stability and developability, marking it as a promising candidate for structure-based antiviral and antibody development.

Keywords: Developability prediction, Electrostatic potential, Epitope mapping, Fab interface, Hydrophobicity, *In silico* modelling.

Correspondence:
Dr. Afaf Salim Alwabli
Department of Biological Sciences, Rabigh College of Science and Arts, King Abdulaziz University, Jeddah-21589, SAUDI ARABIA.
Email: aalwabli@kau.edu.sa

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INTRODUCTION

Dengue is among the most common arthropod-borne viral diseases of humans. Approximately 390 million infections occur each year, of which about one-quarter result in clinical manifestations (Bhatt *et al*., 2013), and roughly half of the world's population now lives in at-risk areas. This risk is amplified by rapid urbanization, global travel and the expansion of *Aedes* mosquitoes driven by climate change (eClinicalMedicine, 2024; Lim *et al*., 2025; Yousuf *et al*., 2024). No effective antiviral therapy is currently available, and existing vaccines show limited efficacy and serotype-dependent safety concerns. Such limitations underscore the importance of validated viral targets that can support both broad protection and serotype-specific intervention (Goh *et al*., 2024; Lim *et al*., 2015). The Dengue Viruses (DENV-1-4) are positive-sense RNA *Flaviviruses* with a genome of ~10.7 kb encoding a single polyprotein that is processed into three structural (C, prM/M, E) and Seven Non-Structural (NS1-NS5) proteins (El Sahili and Lescar, 2017; Murugesan and Manoharan, 2020). Of these, NS5 is the largest and most conserved, and it harbours two enzymatic activities essential for viral replication: an N-terminal methyltransferase domain that also confers guanylyltransferase activity, and a C-terminal RNA-dependent RNA Polymerase (RdRp) domain responsible for *de novo* RNA synthesis (Ackermann and Padmanabhan, 2001; El Sahili and Lescar, 2017; Goh *et al*., 2024). NS5 contributes to genome replication, RNA capping and antagonism of innate immune responses, as well as to remodelling of host-cell architecture, underscoring its central role in the DENV life cycle (El Sahili and Lescar, 2017; Lim *et al*., 2015). Because it is both essential and druggable, the DENV NS5 MTase has been the focus of sustained sequence-based, structural and inhibitor-discovery efforts by our

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group and others (Alwabli and Qadri, 2021; Alwabli *et al*., 2019b, 2019d).

The NS5 MTase domain is located at the N-terminus and comprises approximately 262-265 amino acids across the *Flaviviruses*; in DENV-1-4 it spans 262-263 residues (Zhou *et al*., 2007). It adopts a Rossmann-like fold that binds S-Adenosyl-L-Methionine (SAM) and GTP, and it acts sequentially as a methyltransferase for N7- and 2′-O-methylation of the 5′ cap of viral RNA (Egloff *et al*., 2002; Zhou *et al*., 2007). These reactions generate a type-1 cap structure (m^7GpppA-mRNA) that protects against exonucleases, supports efficient translation and aids evasion of pattern-recognition receptors such as the IFIT proteins (Furuichi and Shatkin, 2000; Ramanathan *et al*., 2016). Biochemical and mutagenesis studies have defined conserved catalytic motifs, comprising a catalytic tetrad (Lys-Asp-Lys-Glu) and a SAM-binding "DxH" motif, together with residues that are critical for MTase activity and viral fitness and that also interact with RNA (Kokkinidis *et al*., 2020; Ribeiro *et al*., 2020; Zhou *et al*., 2007). Crystal structures of the DENV MTase alone, of full-length DENV NS5 and of complexes with capped-RNA fragments are available, revealing the spatial organization of the tandem MTase-RdRp and the conformations relevant to RNA binding and catalysis (Egloff *et al*., 2002; Yap *et al*., 2010; Yap *et al*., 2007). Although the overall sequence identity across the NS5 domain is high, even single-residue changes in solvent-exposed regions or interdomain interfaces may be sufficient to affect protein-protein interactions and to modify antibody binding or local dynamics (Cheng *et al*., 2024; Hannemann *et al*., 2013). Such changes in surface electrostatic and/or hydrophobic properties, or in loop conformation, may alter cofactor affinity, catalytic efficiency or immune recognition without any loss of the catalytic motifs (Du *et al*., 2021; Utto-Ortiz *et al*., 2021).

To explain these features, we carried out a comparative structural and biophysical study of the NS5 MTase domain across all four DENV serotypes, building on our recent serotype-resolved analyses of the DENV-1 (Bukhari, 2026b), DENV-2 (Bukhari, 2026a), DENV-3 (Alwabli, 2026b) and DENV-4 (Alwabli, 2026a) NS5 MTase domains. We first mapped the N-terminal MTase region (~262-263 residues) of the NS5 polyprotein and aligned the four DENV sequences to identify conserved and hypervariable regions (Obi *et al*., 2025). We then generated Fab-antigen interface models for each serotype, dividing residues into four classes: direct contact, surface, near-interface and double Fab interface (Ripoll *et al*., 2021). In our energy and charge heatmaps, all four serotypes were most stable at physiological pH (6.0-8.0) and low ionic strength (≤0.05 M), indicating that electrostatic balance - and hence enzymatic activity - is maintained. Notably, within this window DENV-4 NS5 displayed several advantageous energetic properties, demonstrating intrinsic stability and suitability for structure-guided optimization of ligands and antibodies. By integrating sequence conservation, Fab-interface mapping, surface electrostatics and hydrophobicity, developability metrics and stability landscapes, we provide a single structural-biophysical perspective on the NS5 MTase and identify DENV-4 NS5 as a key scaffold for the rational design of antiviral drugs and antibodies against dengue virus.

MATERIALS AND METHODS

Sequence Retrieval and DENV Serotype Genomes

Full-length genome sequences for DENV-1, DENV-2, DENV-3 and DENV-4 were retrieved from the National Center for Biotechnology Information (NCBI) database, using the reference strains established for DENV-1-4 nucleic-acid testing standards (Nunez *et al*., 2016). The complete viral polyprotein (~3390 aa) was translated from each genome, and the structural (C, M/prM, E) and non-structural (NS1-NS5) proteins were sequentially annotated according to the canonical *Flavivirus* genome map (Chambers *et al*., 1990; Lindenbach and Rice, 2003). For each serotype, NS5 was delimited at its C-terminus using the UniProt/RefSeq annotation, and its N-terminal Methyltransferase (MTase) domain was assigned on the basis of the experimentally solved DENV NS5 structures (Egloff *et al*., 2002; Yap *et al*., 2010; Yap *et al*., 2007) and of our serotype-specific analyses of each domain.

Prediction of Fab-Antigen Interface Residues

Each NS5 MTase model was analysed with protein-protein interface-prediction algorithms trained on antibody-antigen complexes (interface-propensity scoring tools such as InterProSurf (Negi *et al*., 2007) and SPPIDER (Porollo and Meller, 2007). Active residues within high-probability contact patches were identified on the basis of solvent exposure, shape complementarity and interface propensities (Kringelum *et al*., 2013; Negi *et al*., 2007; Porollo and Meller, 2007). Predicted residues were grouped into four categories - direct contact, surface, near-interface and double (chain-chain) Fab interface-and are reported together with the dimensionless interface score returned by the prediction workflow, in which higher values denote greater predicted interface involvement.

Electrostatic and Hydrophobic Surfaces

Three-dimensional models of the NS5 MTase domains of the four DENV serotypes were built by comparative (homology) modelling using the available crystal structures of the dengue NS5 MTase as templates (Alwabli, 2025; Alwabli *et al*., 2019c; Ullah *et al*., 2023). Electrostatic potentials were computed with the Adaptive Poisson-Boltzmann Solver (APBS) using standard protonation states and a ±75 mV scale, then mapped onto solvent-accessible surfaces. The same three-dimensional structures were mapped onto hydrophobicity surfaces derived from the Kyte-Doolittle hydropathy scale, revealing hydrophobic (green) and hydrophilic (purple) patches.

Predictive-Model Scatter Plots

Three developability predictors, based on biophysical descriptors derived from the DENV-1-4 MTase models, were used to estimate the risk of self-association (affinity-capture self-interaction nanoparticle spectroscopy, AC-SINS), non-specific interactions (Poly-Specificity Reagent, PSR) and composite stability/liability (META). Predicted scores were plotted on transformed or experiment-like axes against the clinical-stage biophysical reference distribution (Jain *et al.*, 2017). Because a different serotype is highlighted in each projection, the resulting plots are descriptive comparisons rather than a single ranking.

Energy and Charge Heatmaps

Electrostatic energy and net-charge calculations were performed for the DENV-1-4 NS5 MTase domains to evaluate their electrostatic stability. Calculations were carried out across a range of pH values (2.0-8.0) and ionic strengths (0.005-0.3 M) using the Adaptive Poisson-Boltzmann Solver (APBS) (Konecny *et al.*, 2012). Protonation states were determined using continuum pK_a calculations, which estimate the pH at which protein groups gain or lose protons. Average energy and charge values were displayed as heatmaps with colour gradients denoting favourable or unfavourable electrostatics. This approach enabled comparison of electrostatic patterns between serotypes and identification of conditions under which all serotypes are electrostatically stable.

RESULTS

Overview of DENV Structural Components and the NS5 MTase Domain

Figure 1 shows the structure of the dengue virus and highlights the differences among its four serotypes. The basic architecture of all serotypes comprises an envelope, a lipid membrane, a nucleocapsid and an RNA genome, with virions rendered differently to reveal serotype-specific characteristics. The polyprotein map depicts the structural proteins (Capsid, M, Envelope) and non-structural proteins (NS1, NS2A/NS2B, NS3, NS4A/NS4B and NS5) in relation to the viral genome. The N-terminal region of NS5 is a methyltransferase whose sequence differs slightly among serotypes: 262 amino acids for DENV-1 and DENV-3, and 263 amino acids for DENV-2 and DENV-4 (Figure 1), consistent with the domain boundaries reported in our serotype-specific studies. The figure also emphasizes the conserved position of NS5 and the alignment of the MTase sequences, with only small serotype-dependent differences.

Predicted Fab-Antigen Interface Profiles

Predicted Fab categories for DENV-1 to DENV-4 on NS5 are shown in Figure 2. All serotypes share a red contact region at the same location (interface score 1.78, arbitrary units), followed by blue surface residues (2.87), orange near-interface residues (3.0-3.4) and green chain-chain interface segments (3.88). Each serotype also shows a distinct "peak", that is, the best-scoring position: Pro114 for DENV-1 and DENV-4, Tyr88 for DENV-2 and Ile49 for DENV-3 (Figure 2).

Electrostatic and Hydrophobic Surface Profiles of DENV NS5 MTase

The electrostatic and hydrophobic surface representations of the NS5 MTase domain from the four dengue serotypes are shown in Figure 3. Electrostatic-potential maps (blue, positive charge; red, negative charge; on a +75 to -75 mV scale) are presented in panels a, c, e and g. Each serotype displays blue, white and red patches that vary in the clustering and density of charged regions, producing distinct electrostatic patterns (Figures 3a, 3c, 3e, 3g). The corresponding hydrophobicity surfaces are shown in panels b, d, f and h, with hydrophobic areas in green and hydrophilic areas in purple. The green, white and purple patches are unique to each serotype, with variation in the distribution of hydrophobic and hydrophilic zones; green patches may be clustered or dispersed depending on the NS5 model (Figures 3b, 3d, 3f, 3h). When displayed side by side, the electrostatic (a, c, e, g) and hydrophobicity (b, d, f, h) maps are distinctive for each serotype. The consistent colour scales clearly indicate differences in the location and size of charged and hydrophobic regions, which give rise to different molecular profiles; the electrostatic (left) and hydrophobicity (right) maps are paired for each serotype to facilitate comparison.

Developability Profiling of DENV Serotypes

Figure 4 presents four scatter plots of predicted, transformed and experiment-like values of the NS5 MTase across developability models. In the AC-SINS panels (Figures 4A, 4B), the orange-highlighted DENV-1 and DENV-2 separate toward the upper right. The META panel (Figure 4C) shows DENV-3 highlighted at a high Group-X value in the lower right. In the PSR panel (Figure 4D), the orange-highlighted DENV-4 is separated from the other points, located higher and to the right. In each plot, orange denotes the single serotype highlighted for that model, so the four panels describe complementary projections rather than a common ranking.

Stability Heatmaps of the NS5 MTase

The heatmaps in Figure 5 display the electrostatic energy and net charge of the NS5 MTase domain for the four dengue serotypes across the pH and ionic-strength ranges examined. The energy heatmaps (Figures 5A, 5C, 5E, 5G) show a systematic decrease in electrostatic energy between the acidic region (pH 2.0-4.0) and the near-neutral region (pH 5.0-8.0). In each panel the colour shifts from red/yellow at low pH to green at higher pH, so that higher pH corresponds to lower (more favourable) energy and lower pH to higher, less favourable energy. Warm colours are most pronounced within the acidic region, where the reduced ionic screening at low ionic strength further accentuates the

unfavourable electrostatic term; within the near-neutral window (pH 6.0-8.0), by contrast, the energy surface is uniformly low and reaches its minimum at low ionic strength (≤0.05 M). The corresponding charge heatmaps for each serotype (Figures 5B, 5D, 5F, 5H) are scaled from +0.20 to -0.20 e per residue, with blue denoting positive and red denoting negative net charge. Across the whole grid the domain carries a net positive charge, which is largest in the acidic region and decreases monotonically as the pH rises: the mean net charge falls from approximately +0.18 e per residue at pH 2.0 to approximately +0.04 e per residue at pH 8.0, corresponding to a shift from roughly +47 e to +11 e for a 263-residue domain. The deep blue of the acidic region therefore reflects the large positive charge carried by the domain when its acidic side chains are protonated, and the progressive lightening toward pH 8.0 reflects their stepwise deprotonation. The charge patterns are near-identical across the four serotypes and consistently describe a transition from a strongly positive to a substantially reduced, weakly positive net charge.

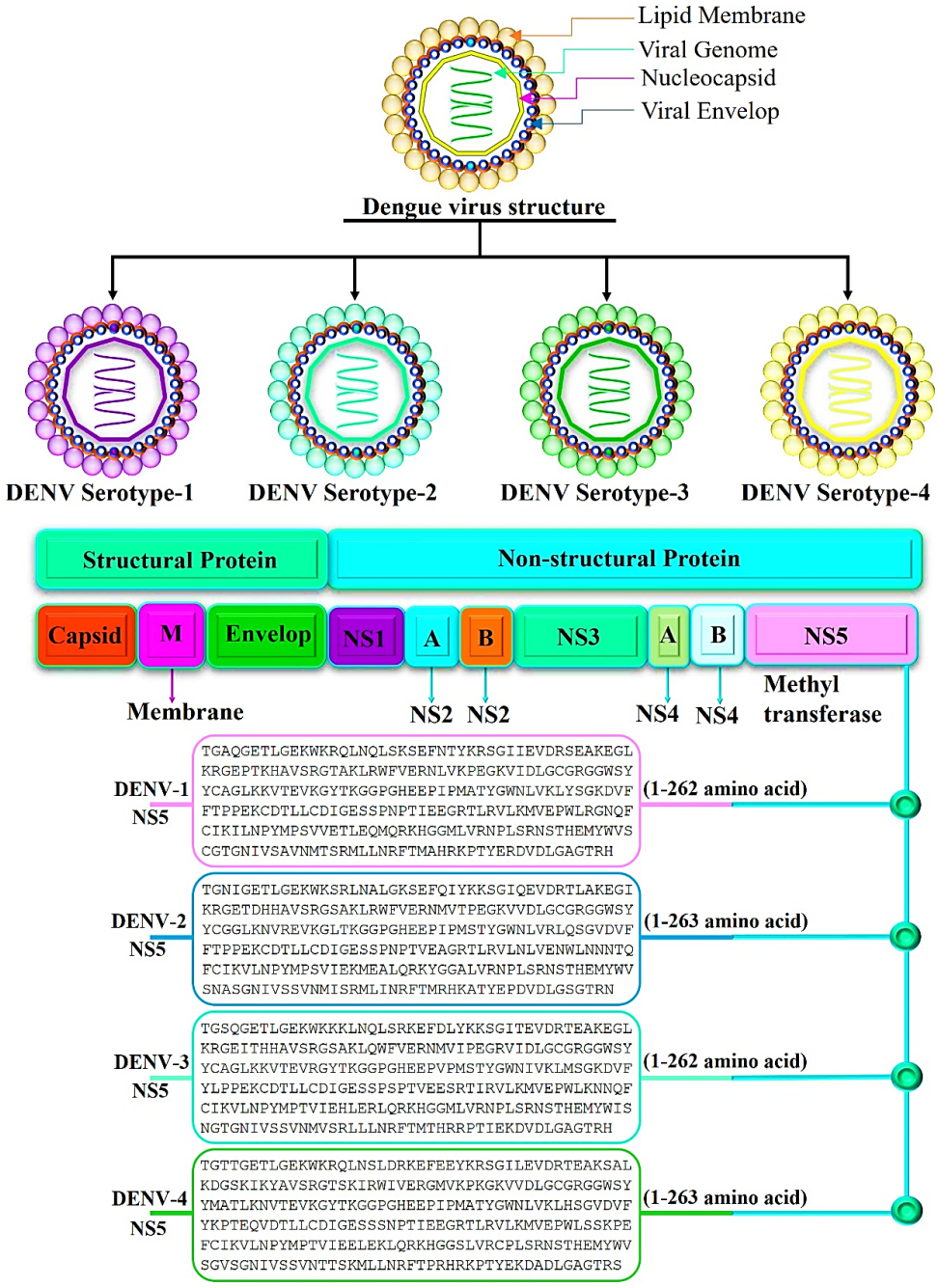

Figure 1: Dengue virus structure and comparative NS5 MTase sequence analysis across DENV-1-4 (262-263 aa). The panel shows the virion architecture (envelope, lipid membrane, nucleocapsid and RNA genome), the polyprotein map of the structural (C, M, E) and non-structural (NS1-NS5) proteins, and the aligned N-terminal MTase sequences of the four serotypes.

DISCUSSION

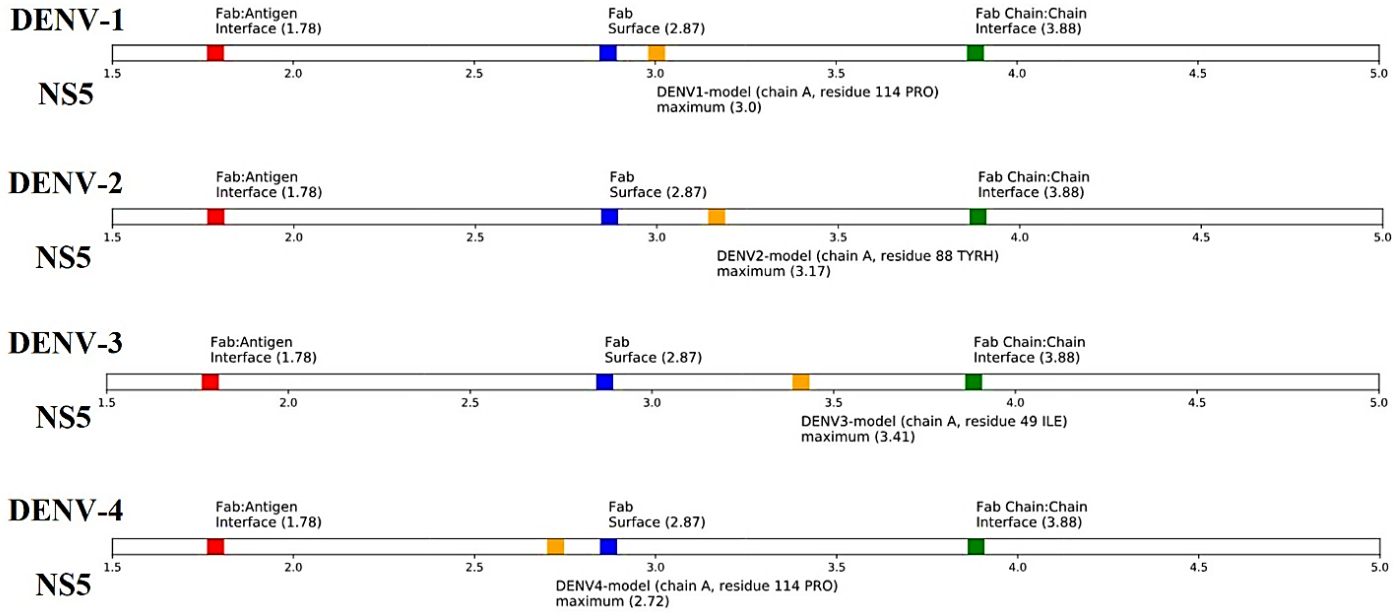

Figure 2: Comparative Fab-antigen interface analysis of the DENV-1-4 NS5 proteins. Residues are coloured by predicted category: direct contact (red), surface (blue), near-interface (orange) and double chain-chain Fab interface (green); values are dimensionless interface scores. Serotype-specific best-scoring contact residues are Pro114 (DENV-1/4), Tyr88 (DENV-2) and Ile49 (DENV-3).

Together, the figures provide a clear picture of the overall conservation of the dengue virus NS5 Methyltransferase (MTase) across serotypes, alongside unique surface and developability characteristics that can be exploited for targeting. NS5 is among the most conserved and essential proteins of dengue virus. Its N-terminal MTase domain performs both the N7 and 2′-O methylation steps of RNA capping and is tightly coupled to the C-terminal polymerase domain (Byszewska *et al*., 2014; Egloff *et al*., 2002). This central role is reflected in the very similar overall architecture of the serotypes shown in Figure 1: all share the same genome organization, with NS5 at the C-terminal end of the polyprotein, and residues across the ~262-263-aa domain are well conserved. This is consistent with previous structural studies of the DENV NS5 MTase, in which specific substitutions modulate local interactions while the main catalytic motifs are preserved (Egloff *et al*., 2002; Norazharuddin and Lai, 2018).

The predicted Fab-antigen interaction categories along NS5 are similar for all serotypes, each conveying a primary Fab-contact region together with Fab-exposed surface, near-interface and Fab chain-chain interface regions. This indicates a conserved epitope architecture within NS5. Figure 2 also identifies specific interface residues that are key serotype-specific determinants - Pro114 for DENV-1/4, Tyr88 for DENV-2 and Ile49 for DENV-3 - that form "hotspots" at these interfaces, in agreement with the serotype-specific interface and epitope features we mapped individually (Alwabli, 2026a, 2026b; Bukhari, 2026a, 2026b). Because antibody binding may be serotype-biased at these residues, they offer rational targets for the design of serotype-specific or serotype-broadening, epitope-focused antibodies or immunogens (Sadraeian *et al*., 2024).

Although the electrostatic and hydrophobic patches are broadly similar between serotypes, their combination differs for each NS5 MTase, as evidenced by the surface maps in Figure 3. Mosaics of positive and negative electrostatic potential are found across all serotypes when computed with the Adaptive Poisson-Boltzmann Solver (APBS) (Jurrus *et al*., 2018; Ren *et al*., 2012), but the size and location of high-potential clusters vary. The paired hydrophobicity surfaces are similarly conserved in overall structure, with a more serotype-specific distribution of hydrophobic (green) and hydrophilic (purple) patches. Because RNA binding, cofactor binding and antibody binding are all influenced by surface electrostatics and hydrophobicity, these patterns suggest that the local environment of the same catalytic site may differ between serotypes, affecting affinity and selectivity (Potisopon *et al*., 2014).

The structural descriptors were used for developability-style measurements, with NS5-derived features serving as surrogates in AC-SINS-like, META-like and PSR-like spaces. In each plot, the highlighted serotype (orange) is plotted against many reference molecules. AC-SINS is a widely used assay for evaluating self-association and colloidal stability of antibodies during discovery; META is a composite of several biophysical readouts; and Poly-Specificity Reagent (PSR) assays, or related methods, report the propensity for non-specific interactions (Jain *et al*., 2017; Liu *et al*., 2014; Xu *et al*., 2013). Read together, these projections indicate that each serotype occupies a distinct

region of developability space rather than that any one serotype is uniformly superior: DENV-1 and DENV-2 are displaced in the AC-SINS-like projection, DENV-3 in the META-like projection and DENV-4 in the PSR-like projection. Because each panel highlights a different serotype against the same reference set, the comparison is descriptive rather than a ranking, and the favourable position of DENV-4 in the PSR-like space should be read as a model-specific indication of low predicted non-specificity rather than as a global developability advantage.

Figure 5 places the physicochemical stability of the NS5 MTase in context. Electrostatic energy is highest at acidic pH and decreases toward neutrality for all four serotypes, with minimum

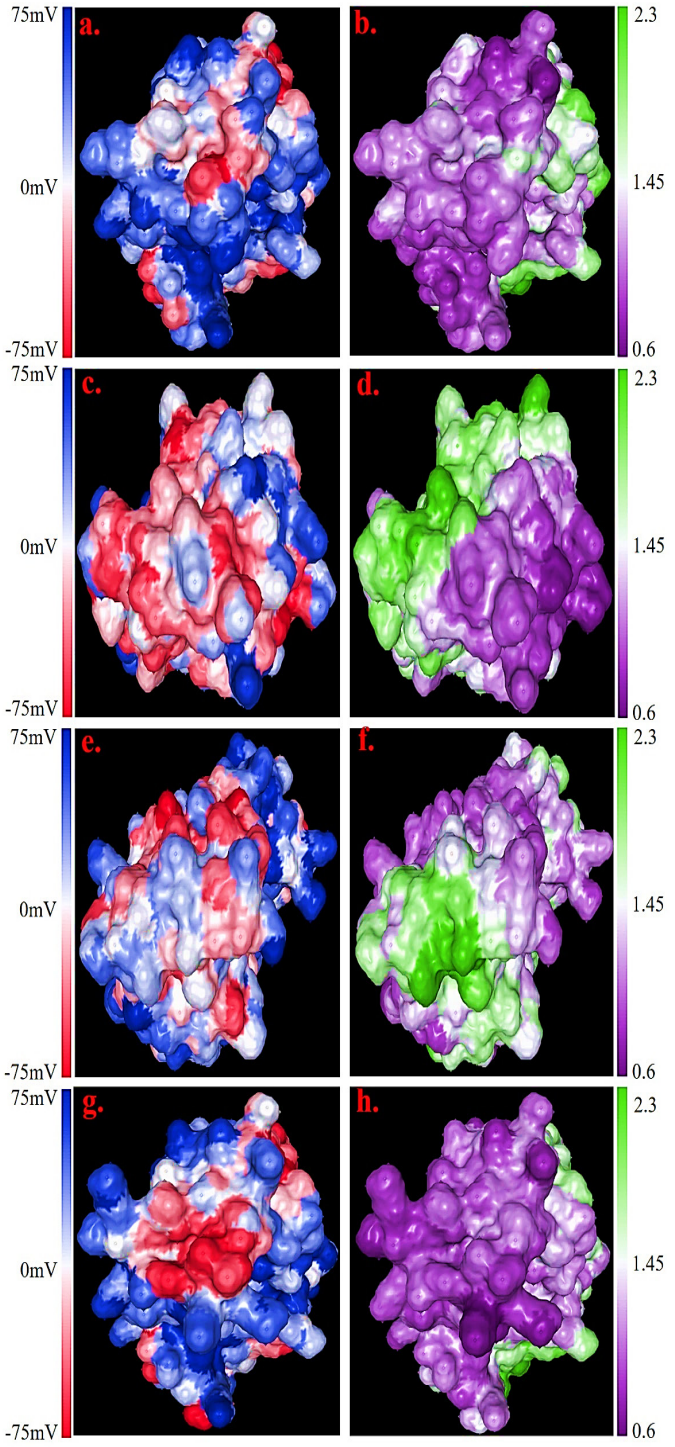

Figure 3: Electrostatic and hydrophobic surface maps of the DENV-1-4 NS5 MTase domains. Panels (a, c, e, g) show electrostatic-potential maps on a +75 to -75 mV scale (blue, positive; red, negative); panels (b, d, f, h) show Kyte-Doolittle hydrophobicity maps (green, hydrophobic; purple, hydrophilic).

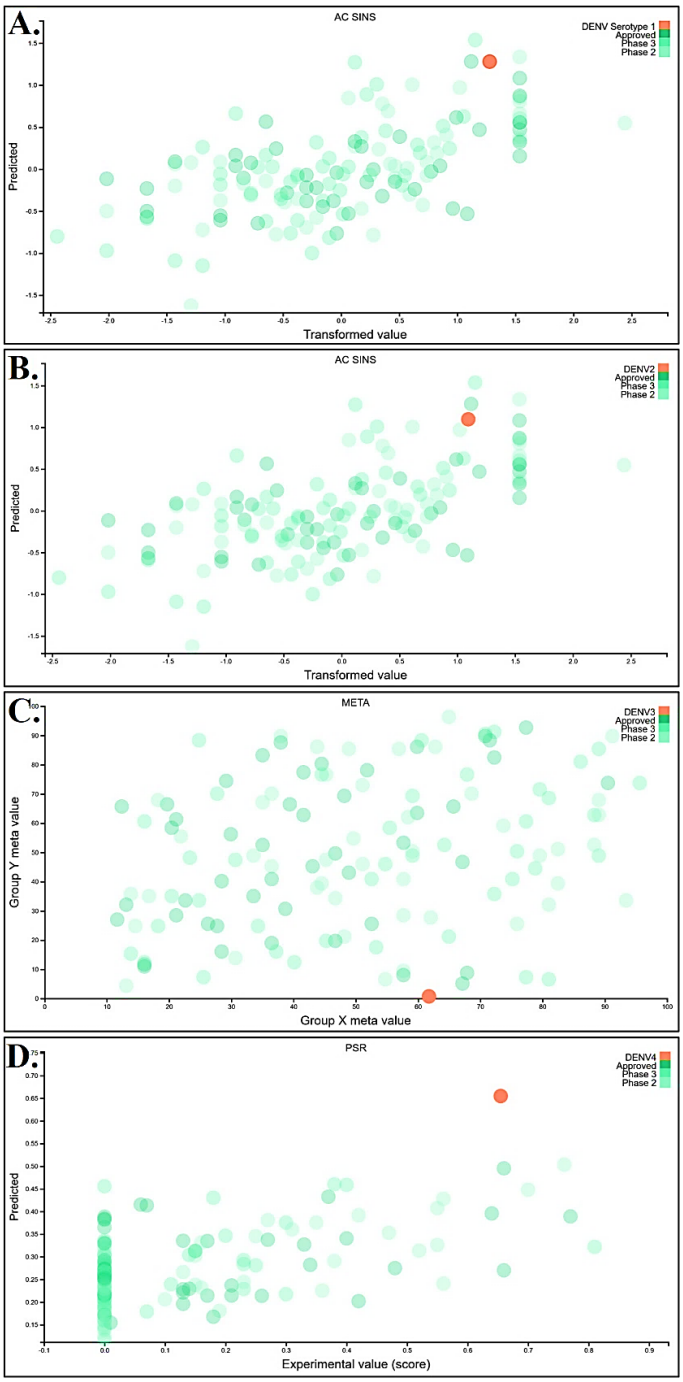

Figure 4: Predicted and experiment-like developability projections of the NS5 MTase across the DENV serotypes, plotted against the clinical-stage biophysical reference distribution. Panels (A, B) AC-SINS-like space; panel (C) META-like space; panel (D) PSR-like space. In each panel, orange denotes the single serotype highlighted for that model; the panels are therefore complementary projections rather than a common ranking. DENV-4 separates most clearly in the PSR-like projection.

(most favourable) values around pH 6-8 and low ionic strength. Consistent with this, the charge maps show a large net positive charge at low pH (≈ +0.18 e per residue at pH 2.0) that converges toward a tight, weakly positive band (≈ +0.04 e per residue) over the same interval - the behaviour expected as the acidic side chains of the domain become progressively deprotonated. All serotypes share a similar electrostatic-stability window at mildly acidic-to-neutral pH and low salt concentration; within this window, the energy landscape is particularly flat for some serotypes, including DENV-4, indicating tolerance to small changes in pH and ionic strength. These *in silico* findings complement ongoing structure-guided and phytochemical inhibitor-discovery efforts against dengue and related flaviviral targets (Alwabli, 2022, 2023; Alwabli *et al*., 2025; Patel *et al*., 2022) and broader molecular-profiling studies of dengue infection (Alwabli, 2024; Alwabli *et al*., 2019a), and support the DENV-4 NS5 MTase as

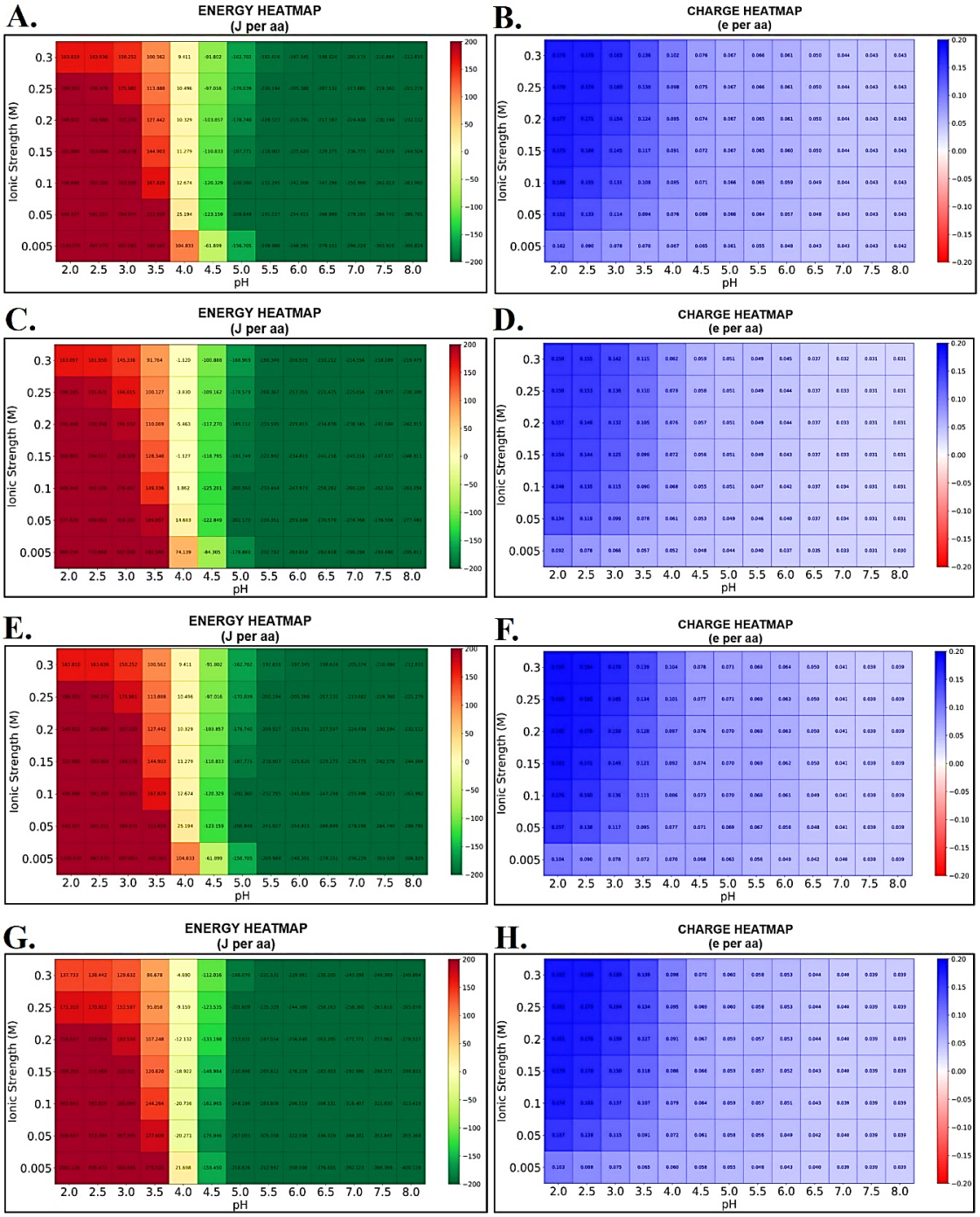

Figure 5: Electrostatic energy (J per residue; panels A, C, E, G) and net charge (e per residue; panels B, D, F, H) heatmaps for DENV-1 to DENV-4 as a function of pH (2.0-8.0) and ionic strength (0.005-0.3 M). In the energy panels, warm colours denote higher (less favourable) energy and cool colours denote lower (more favourable) energy. In the charge panels the colour convention matches Figure 3: blue denotes positive net charge and red denotes negative net charge.

a priority scaffold. Nonetheless, because the present results are computational, experimental testing of binding, enzymatic activity and formulation properties is still required before the NS5 MTase-specifically that of DENV-4 - can be established as a target scaffold for antiviral or antibody development.

CONCLUSION

The results indicate that the NS5 methyltransferase domain is highly conserved yet adaptable across the four dengue virus serotypes. The polyprotein map and NS5 alignments show that the N-terminal MTase region has retained its size and position (262-263 aa), strongly indicating an essential role in the DENV life cycle. Fab-interface mapping and surface analysis further reveal serotype-specific features - unique Fab-contact hotspots, electrostatic patches and hydrophobic clusters - within this conserved core. These features offer practical opportunities for developing serotype-specific or broad-spectrum antiviral strategies, targeting one or multiple serotypes as required. On developability parameters, each NS5 MTase has a distinct profile relative to reference biotherapeutics, and DENV-4 stands out in the PSR-like space. The energy and charge heatmaps show that the electrostatic profile of the four MTase domains remains stable at low ionic strength and pH 6-8, suggesting that NS5 is well suited to intracellular environments and to formulation in an appropriate buffer. Among the four serotypes, DENV-4 shows the flattest energy landscape within this window and is therefore an attractive choice for recombinant-antigen production and for the optimization of ligands and antibodies. We conclude that the DENV-4 NS5 MTase warrants priority evaluation in recombinant-antigen development pipelines, alongside parallel DENV-4 ligand- and antibody-optimization studies based on its specific characteristics.

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ABBREVIATIONS

aa: Amino Acids; **AC-SINS:** Affinity-Capture Self-Interaction Nanoparticle Spectroscopy; **APBS:** Adaptive Poisson-Boltzmann Solver; **DENV:** Dengue Virus; **Fab:** Fragment Antigen-Binding; **IFIT:** Interferon-Induced Protein with Tetratricopeptide repeats; **META:** Composite Biophysical Developability Metric; **MTase:** Methyltransferase; **NCBI:** National Center for Biotechnology Information; **NS5:** Non-Structural Protein 5; **pH:** Potential of Hydrogen; **PSR:** Poly-Specificity Reagent (assay); **RdRp:** RNA-dependent RNA Polymerase; **SAM:** S-Adenosyl-L-Methionine; **SPPIDER:** Solvent accessibility-based Protein-Protein Interface iDEntification and Recognition.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

FUNDING

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AUTHOR CONTRIBUTIONS

Afaf Salim Alwabli: Conceptualization; Methodology; Data curation; Formal analysis; Investigation; Writing - original draft. **Ghadeer Fareed Bukhari:** Methodology; Formal analysis; Investigation; Writing - review and editing. Both authors have read and approved the final manuscript.

SUMMARY

The NS5 methyltransferase domain is highly conserved across the four dengue virus serotypes yet retains distinct structural and biophysical features. DENV-4 exhibited the most favourable predicted developability, electrostatic stability and surface properties of all serotypes, with a particular advantage under physiologically relevant conditions. These findings indicate that DENV-4 NS5 is a promising candidate for recombinant-antigen development and a high-priority target for structure-guided optimization of ligands and antibodies.

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