## Supplementary Information

# Glycoprotein Attachment with Host Cell Surface Receptor Ephrin B2 and B3 in Mediating Entry of Nipah and Hendra Virus: A Computational Investigation

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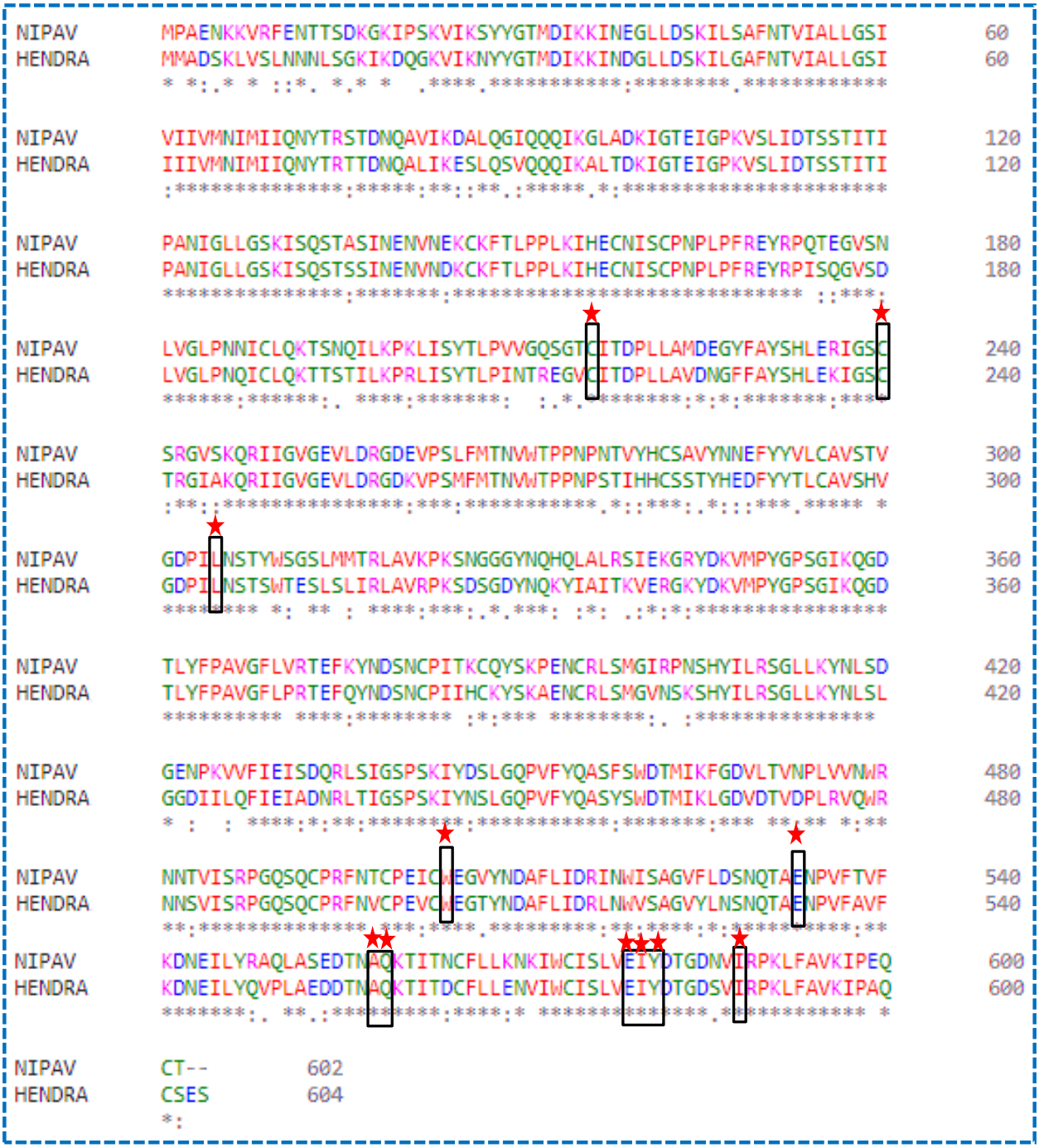
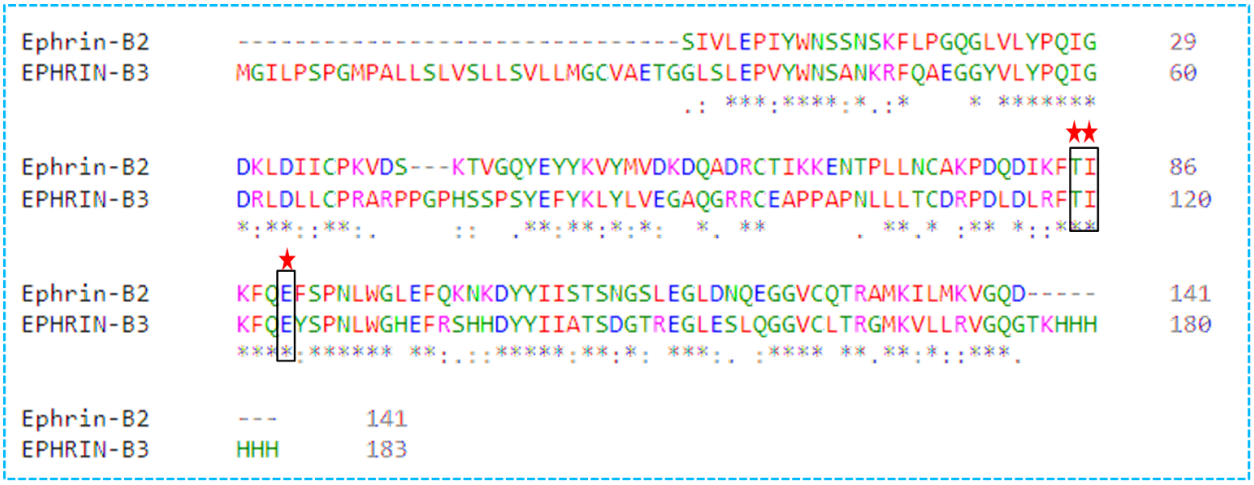



"*" Fully conserved ":" Conservation between groups of amino acids with strongly similar properties "." Conservation between groups of amino acids with weakly similar properties

**Figure S1:** Sequence alignment of NiV glycoprotein (602AA) and HeV glycoprotein (604 AA) with 539/604 (89.2%) sequence similarity and 474/604 (78.5%) sequence identity among both the sequences. The analysis was carried out using Clustal Omega. The interface residues present in the conserved region of both the NiV and HeV glycoproteins are highlighted in box with star mark.




"*" Fully conserved ":" Conservation between groups of amino acids with strongly similar properties "." Conservation between groups of amino acids with weakly similar properties

**Figure S2:** Sequence alignment of human cell surface protein EphrinB2 (144AA) and EphrinB3 (183AA) with 53% sequence similarity and 38.7% sequence identity among both the sequences. The sequence analysis was carried out using Clustal Omega. The interface residues present in the conserved region of both the EFNs are highlighted in box with star mark.

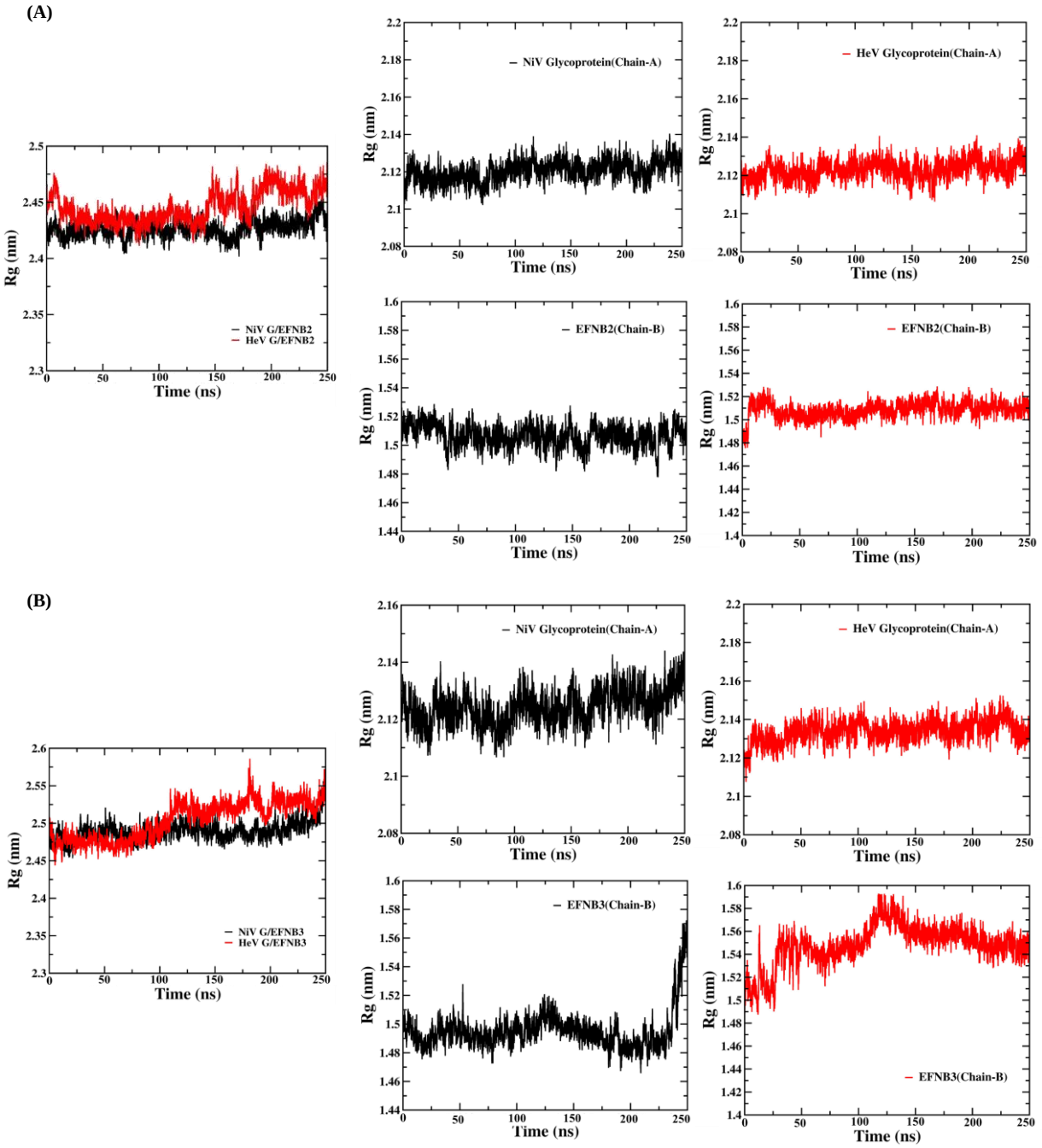



**Figure S3:** Radius of gyration (Rg) of each chain of the PPI complexes (A) NiV glycoprotein (Chain-A)/EFNB2 (Chain-A) and HeV glycoprotein (Chain-A)/EFNB2 (Chain-B) (B) NiV glycoprotein (Chain-A)/EFNB3 and HeV glycoprotein (Chain-A)/EFNB3 in the course of 250 ns MD simulation

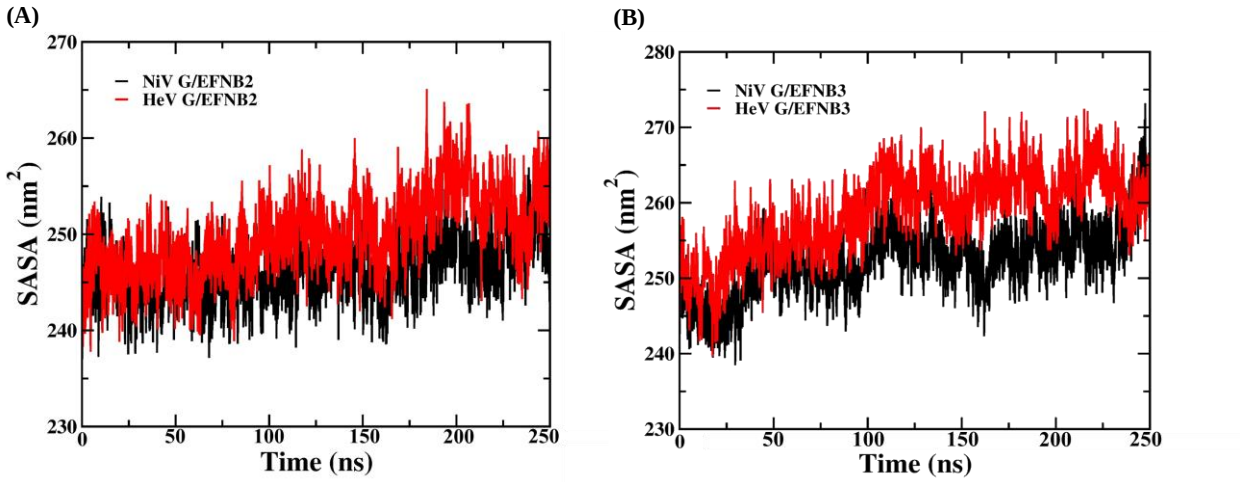



**Figure S4:** Solvent Accessible Surface Area (SASA) graph of the simulation protein complexes of NiV and HeV virus glycoprotein in complex with human cell surface proteins EFNB2-B3. The NiV complex in both the graphs is represented in black colour and the HeV complex in both the graphs is represented in red colour

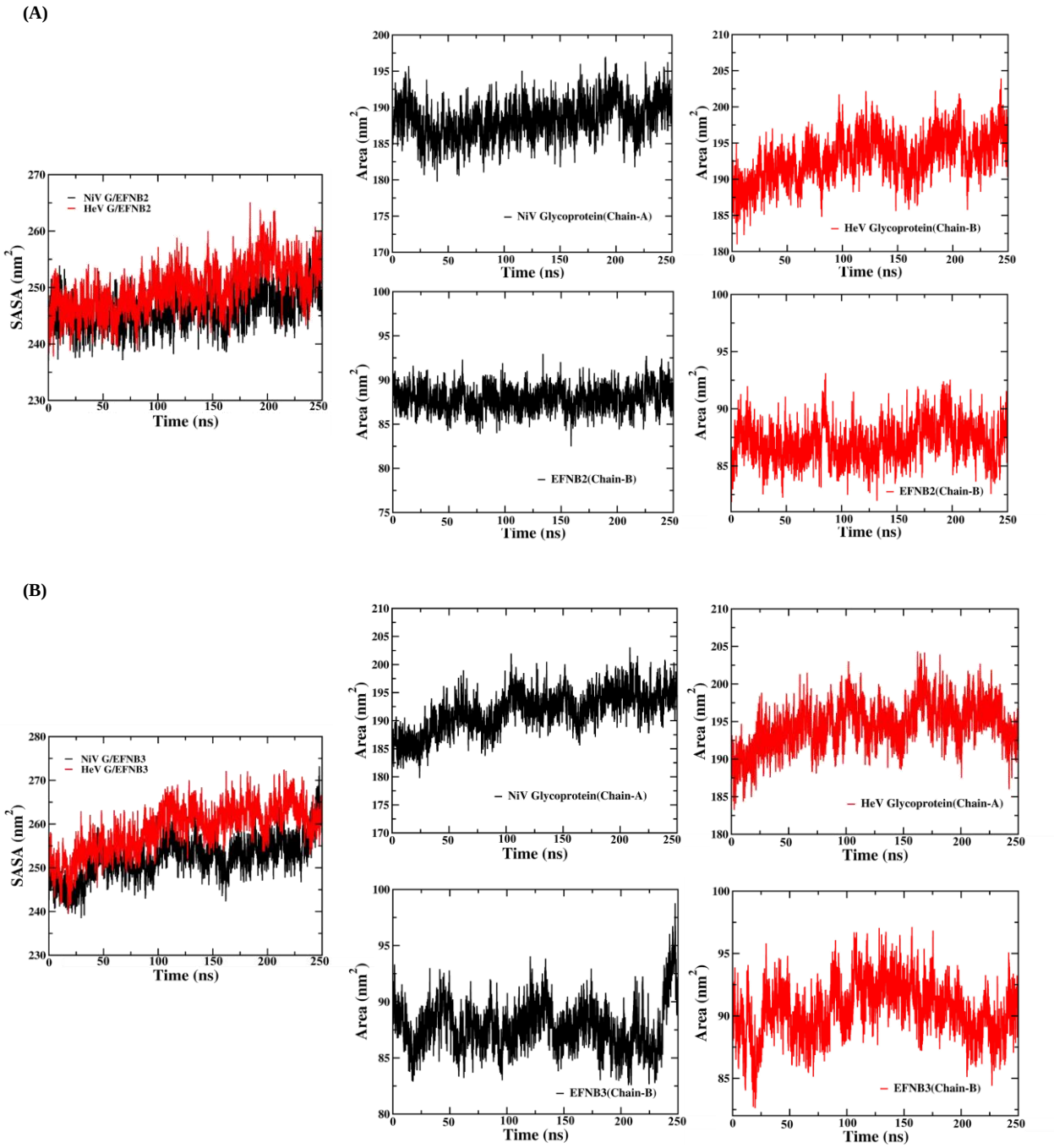



**Figure S5:** Solvent Accessible Surface Area (SASA) of each chain of the PPI complexes (A) NiV glycoprotein (Chain-A)/EFNB2 (Chain-A) and HeV glycoprotein (Chain-A)/EFNB2 (Chain-B) (B) NiV glycoprotein (Chain-A)/EFNB3 and HeV glycoprotein (Chain-A)/EFNB3 in the course of 250 ns MD simulation.

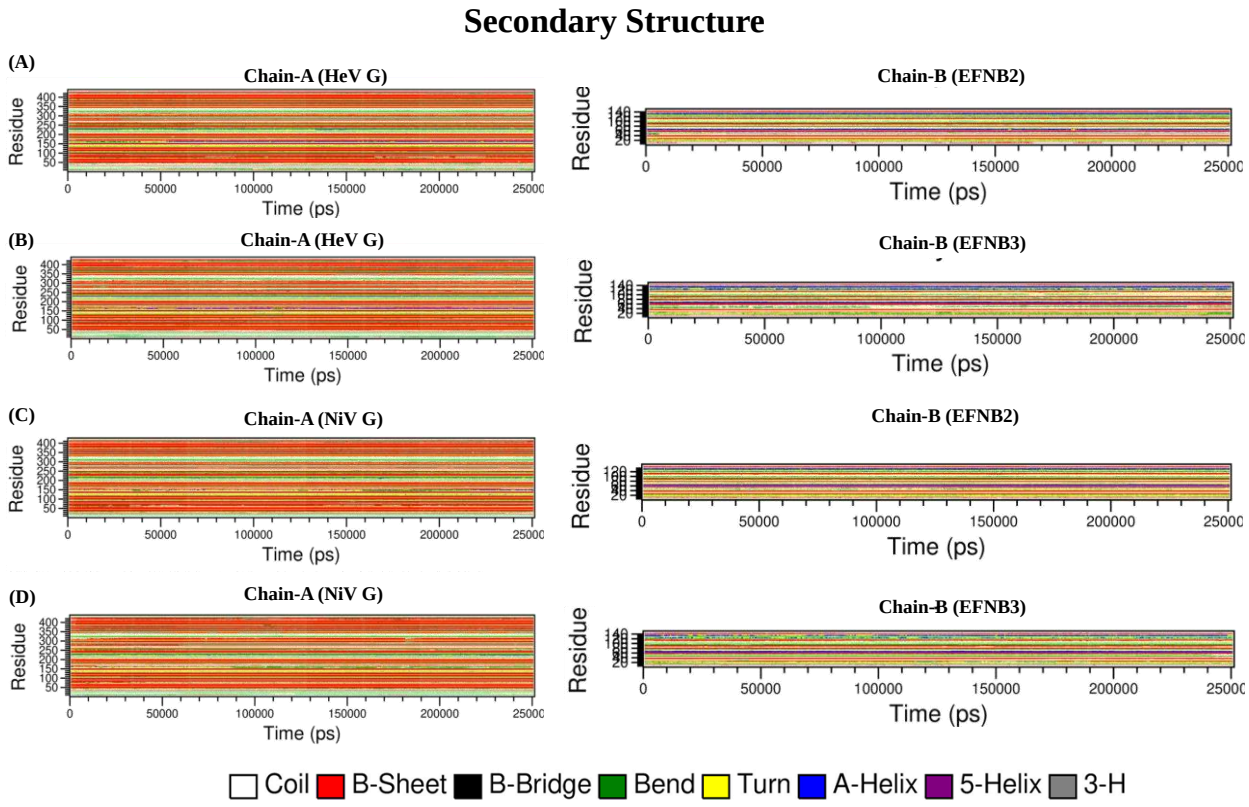



**Figure S6:** Secondary structure analysis of (A) HeV glycoprotein and human EFNB2 (B) HeV glycoprotein and human EFNB3 (C) NiV glycoprotein and human EFNB2 (D) NiV glycoprotein and human EFNB3 during the course of 250 ns MD simulation has been shown using the DSSP algorithm. The colour code representing the structures has been shown on the right of the graph.

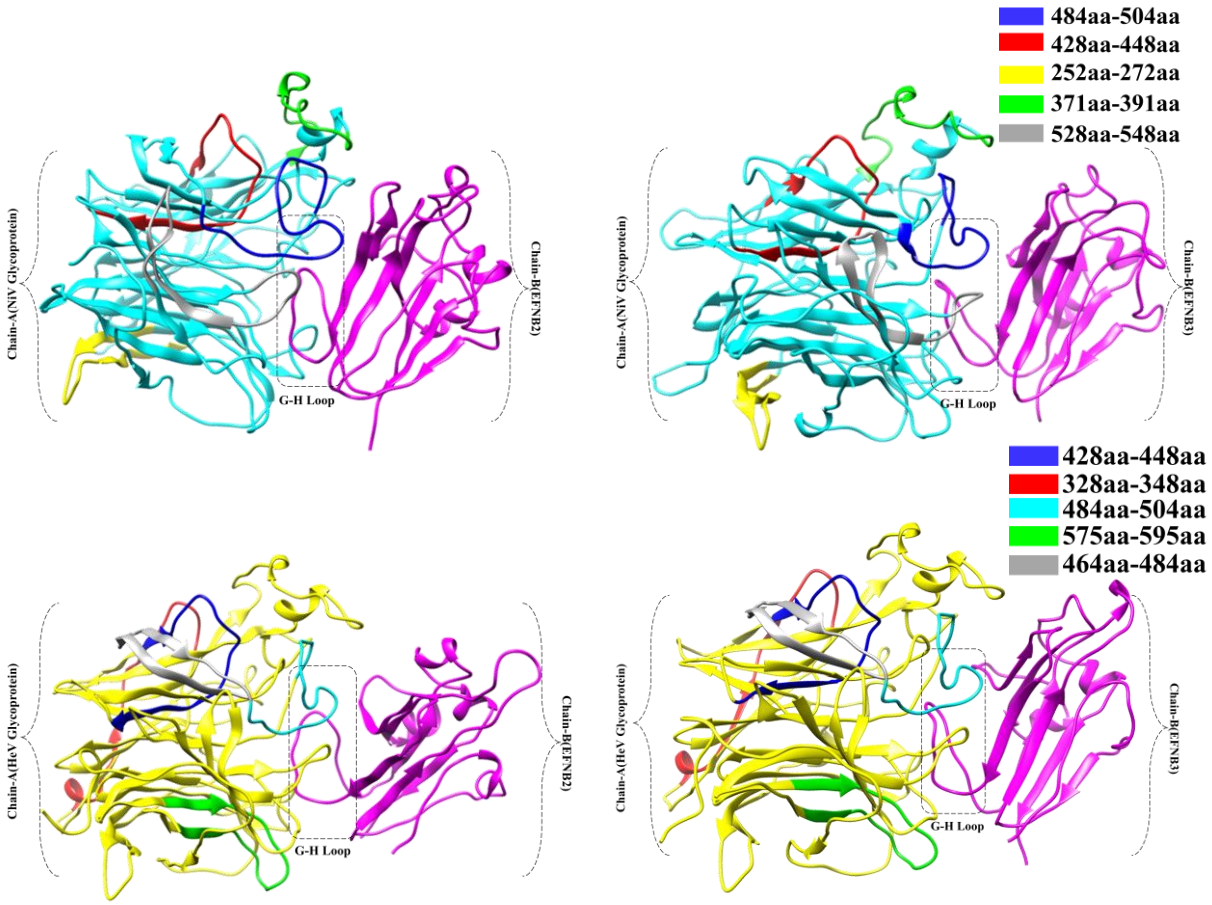



**Figure S7:** Representation of linear predicted B cell epitopes highlighted in the protein structure of (A) NiV glycoprotein/EFNB2, (B) NiV glycoprotein/EFNB3, (C) HeV glycoprotein/EFNB2 and (D) HeV glycoprotein/EFNB3. The stretch of epitopes (amino acid range) consisting of 20 amino acids are highlighted with different colors respectively.

**Table S1:** Comparison of interface statistics of the selected virus-host initial before MD) PPI complexes with the average complex structures extracted from 0-50 ns, 50-100 ns, 100-200 ns, 200-250 ns trajectories. Interface profile information was obtained from PDBsum server.

| **PPI complexes** | **PPI profile** | | **Initial structure** | **0-50 ns** | **50-100 ns** | **100-150 ns** | **150-200 ns** | **200-250 ns** |
|---|---|---|---|---|---|---|---|---|
| NiV-glycoprotein /EFNB2 | No. of H-bonds | | 21 | 17 | 15 | 12 | 10 | **16** |
| | No. of salt bridges | | 3 | 2 | 2 | 2 | 4 | **4** |
| | Non-bonded contacts | | 218 | 130 | 114 | 104 | 113 | **141** |
| | No. of interface residues | Chain A | 32 | 25 | 22 | 23 | 22 | **24** |
| | | Chain B | 27 | 22 | 20 | 21 | 21 | **23** |
| | Interface area | Chain A | 1373 | 1353 | 1234 | 1218 | 1262 | **1219** |
| | | Chain B | 1473 | 1426 | 1300 | 1284 | 1316 | **1257** |
| NiV-glycoprotein /EFNB3 | No. of H-bonds | | 11 | 4 | 7 | 4 | 4 | **6** |
| | No. of salt bridges | | 4 | 2 | 2 | 2 | 2 | **1** |
| | Non-bonded contacts | | 127 | 95 | 85 | 75 | 83 | **73** |
| | No. of interface residues | Chain A | 24 | 22 | 24 | 25 | 25 | **20** |
| | | Chain B | 19 | 17 | 16 | 16 | 15 | **12** |
| | Interface area | Chain A | 997 | 1050 | 1058 | 1047 | 1034 | **934** |
| | | Chain B | 1166 | 1180 | 1206 | 1198 | 1176 | **1089** |
| HeV-glycoprotein / EFNB2 | No. of H-bonds | | 12 | 11 | 21 | 14 | 14 | **11** |
| | No. of salt bridges | | 4 | 3 | 3 | 3 | 4 | **2** |
| | Non-bonded contacts | | 160 | 105 | 131 | 116 | 109 | **75** |
| | No. of interface residues | Chain A | 30 | 26 | 26 | 24 | 23 | **20** |
| | | Chain B | 26 | 22 | 24 | 21 | 18 | **16** |
| | Interface area | Chain A | 1300 | 1197 | 1277 | 1168 | 1150 | **1123** |
| | | Chain B | 1389 | 1266 | 1335 | 1274 | 1245 | **1210** |
| HeV-glycoprotein / EFNB3 | No. of H-bonds | | 12 | 4 | 7 | 4 | 4 | **6** |
| | No. of salt bridges | | 5 | 2 | 2 | 2 | 2 | **1** |
| | Non-bonded contacts | | 137 | 95 | 85 | 75 | 83 | **73** |
| | No. of interface residues | Chain A | 26 | 22 | 24 | 25 | 23 | **20** |
| | | Chain B | 26 | 17 | 16 | 16 | 15 | **12** |
| | No of interface area | Chain A | 1184 | 1050 | 1058 | 1047 | 1034 | **934** |
| | | Chain B | 1272 | 1180 | 1206 | 1198 | 1176 | **1089** |

NiV: Nipah Virus, HeV: Hendra virus, EFN: Ephrin

**Table S2:** PBC cubic box information for NiV glycoprotein /EFN B2, NiV glycoprotein /EFN B3, HeV glycoprotein /EFNB2 and HeV glycoprotein /EFN B3.

| **PBC Box information** | **NiV glycoprotein /EFN B2** | | | **NiV glycoprotein /EFN B3** | | | **HeV glycoprotein /EFN B2** | | | **HeV glycoprotein /EFN B3** | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **x** | **y** | **z** | **x** | **y** | **z** | **x** | **y** | **z** | **x** | **y** | **z** |
| **Box vectors/size (nm)** | 6.328 | 6.311 | 7.183 | 8.167 | 6.209 | 5.646 | 5.910 | 7.688 | 6.236 | 8.126 | 6.101 | 5.521 |
| **Box volume ($nm^3$)** | | 286.88 | | | 286.31 | | | 283.34 | | | 273.69 | |
| **System size (nm)** | 6.328 | 6.311 | 7.183 | 8.167 | 6.209 | 5.646 | 5.910 | 7.688 | 6.236 | 8.127 | 6.101 | 5.521 |
| **Diameter (nm)** | | 8.442 | | | 8.506 | | | 8.695 | | | 8.527 | |

**Table S3:** List of interacting residues at protein-protein interacting interface of initial structures of NiV and HeV glycoprotein (chain A) in complex with human EFNB3/B3(chain B) each. The interface hotspot residues were predicted using three computational methods implemented in KFC2 server, and Robetta web server. The per-residue energy decomposition analysis was carried out using the pyDockEneRes Server

| Complex | Residues (Pre MD) | KFC2 server | DrugScore PPI (KJ/mol) | Robetta ΔΔG (KJ/mol) | Per-residue energy contribution (KJ/mol) |
|---|---|---|---|---|---|
| **NiV glycoprotein /EFNB2** | Gln490-A | HS | 5.0 | 8.3 | -5.2 |
| | Gln530-A | HS | 3.6 | 12.3 | -6.8 |
| | Trp504-A | HS | 6.8 | 10.5 | -24.5 |
| | Arg242-A | - | 4.4 | 4.1 | -5.2 |
| | Glu533-A | HS | 2.9 | 9.6 | 5.9 |
| | Asn557-A | HS | 4.6 | 5.7 | -5.1 |
| | Tyr581-A | HS | 11.6 | 15.3 | -26.6 |
| | Asn123-B | - | 3.7 | 3.0 | 1.3 |
| | Phe113-B | HS | 2.8 | 5.0 | -21.5 |
| | Leu124-B | HS | 10.1 | 11.9 | -43.6 |
| | Trp125-B | HS | 7.5 | 13.0 | -50.4 |
| | Lys116-B | HS | 4.9 | 9.4 | -1.2 |
| | Gln118-B | HS | 4.1 | 7.0 | -18.0 |
| | Glu119-B | HS | 2.8 | 3.4 | -11.8 |
| | Glu128-B | HS | 4.8 | 9.4 | -17.6 |
| | Phe120-B | HS | 8.3 | 21.1 | -81.9 |
| **NiV glycoprotein /EFNB3** | Thr531-A | HS | 1.7 | 2.8 | -21.6 |
| | Asn557-A | HS | 4.6 | 12.0 | -31.4 |
| | Gln490-A | HS | 5.0 | 7.5 | -27.1 |
| | Ser491-A | HS | 1.8 | 4.4 | 7.6 |
| | Tyr120-B | HS | 8.3 | 15.1 | -94.4 |
| | Glu119-B | HS | 2.8 | 11.9 | -12.2 |
| | Gln118-B | HS | 4.1 | 3.1 | -8.4 |
| | Leu124-B | HS | 10.1 | 9.7 | -78.1 |
| | Lys116-B | HS | 4.9 | 10.4 | 52.9 |
| | Trp125-B | HS | 7.5 | 16.6 | -78.5 |
| | Phe113-B | HS | 2.8 | 7.0 | -39.1 |
| **HeV glycoprotein /EFNB2** | Tyr581-A | - | 10.7 | 6.7 | -67.4 |
| | Asn557-A | HS | 4.6 | 7.8 | -17.1 |
| | Thr531-A | HS | 1.8 | 14.1 | -16.2 |
| | Glu533-A | HS | 2.6 | 9.4 | -42.1 |
| | Trp504-A | - | 6.4 | 9.0 | -34.9 |
| | Glu505-A | HS | | -0.4 | -45.1 |
| | Tyr389-A | - | 18.8 | 10.8 | -32.1 |

| | | | | | |
|---|---|---|---|---|---|
| | Gln490-A | HS | 6.3 | 4.7 | -2.3 |
| | Gln530-A | HS | 3.3 | 8.2 | -8.1 |
| | Lys113-B | HS | 4.4 | 4.9 | -19.0 |
| | Ser118-B | HS | 0.9 | 11.0 | -8.7 |
| | Pro119-B | HS | | 8.6 | -10.9 |
| | Asn120-B | HS | 3.9 | 17.5 | -36.0 |
| | Leu124-B | HS | 1.3 | 9.0 | -5.1 |
| **HeV glycoprotein /EFNB3** | Gln490-A | HS | 5.2 | 4.7 | -8.8 |
| | Glu533-A | HS | 2.1 | 9.4 | -22.9 |
| | Asn557-A | HS | 2.0 | 7.8 | 4.0 |
| | Tyr581-A | HS | 5.8 | 6.7 | -5.5 |
| | Thr531-A | HS | 2.4 | 14.1 | -6.3 |
| | Gln530-A | HS | 3.1 | 8.2 | -24.7 |
| | Glu119-B | HS | 3.9 | 8.6 | -11.7 |
| | Gln118-B | HS | 1.6 | 11.0 | -13.5 |
| | Lys116-B | HS | 4.5 | 0.6 | -18.0 |
| | Tyr120-B | HS | 22.9 | 17.5 | -64.1 |
| | Thr114-B | HS | 0.8 | 4.1 | -6.7 |
| | Leu124-B | HS | 7.2 | 9.0 | -39.7 |
| | Phe113-B | HS | 2.2 | 4.9 | -21.9 |

**Table S4:** Average values of the RMSD, Rg, SASA and the total number of intermolecular hydrogen bond formed for the NiV and HeV virus glycoprotein both in complex with EFNB2 and EFNB3 each.

| Complex | RMSD (nm) | RMSF (nm) | Rg (nm) | SASA (nm) | H-bonds |
|---|---|---|---|---|---|
| **NiV glycoprotein /EFNB2** | 0.14 | Chain A 0.10<br>Chain B 0.10 | 2.0 | 246 | 12 |
| **NiV glycoprotein /EFNB3** | 0.18 | Chain A 0.11<br>Chain B 0.14 | 2.1 | 252 | 9 |
| **HeV glycoprotein /EFNB2** | 0.20 | Chain A 0.11<br>Chain B 0.11 | 2.1 | 249 | 12 |
| **HeV glycoprotein /EFNB3** | 0.28 | Chain A 0.11<br>Chain B 0.16 | 2.1 | 258 | 10 |

**Table S5:** Total number of H-bond involved in the initial structure of NiV glycoprotein/EFNB2 complex. The interface H-bond results obtained from PDBsum server.

| | ATOM 1 (NiV Glycoprotein) | | | | | ATOM 2 (Ephrin B2) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Complex** | **Atom no.** | **Atom name** | **Res name** | **Res no.** | **Chain** | **Atom no.** | **Atom name** | **Res name** | **Res no.** | **Chain** | **Distance** |
| **NiV glycoprotein /EFNB2** | 399 | OG | SER | 239 | A | 4090 | OE2 | GLU | 128 | B | 2.54 |
| | 400 | N | CYS | 240 | A | 4014 | OE1 | GLU | 119 | B | 2.77 |
| | 406 | N | SER | 241 | A | 4089 | OE1 | GLU | 128 | B | 2.93 |
| | 411 | OG | SER | 241 | A | 4089 | OE1 | GLU | 128 | B | 2.97 |
| | 422 | NH2 | ARG | 242 | A | 4059 | O | TRP | 125 | B | 2.87 |
| | 1563 | NE2 | GLN | 388 | A | 3917 | OD2 | ASP | 108 | B | 2.83 |
| | 1575 | OH | TYR | 389 | A | 3916 | OD1 | ASP | 108 | B | 2.58 |
| | 2377 | OE1 | GLN | 490 | A | 4047 | ND2 | ASN | 123 | B | 2.83 |
| | 2384 | OG | SER | 491 | A | 3946 | O | LYS | 112 | B | 3.25 |
| | 2393 | NE2 | GLN | 492 | A | 3881 | OD1 | ASN | 103 | B | 3.3 |
| | 2465 | OE2 | GLU | 501 | A | 3902 | NZ | LYS | 106 | B | 2.59 |
| | 2503 | N | GLY | 506 | A | 4036 | O | PRO | 122 | B | 2.92 |
| | 2701 | OE1 | GLN | 530 | A | 3963 | N | THR | 114 | B | 2.85 |
| | 2702 | NE2 | GLN | 530 | A | 3946 | O | LYS | 112 | B | 2.85 |
| | 2713 | O | ALA | 532 | A | 4006 | NE2 | GLN | 118 | B | 2.96 |
| | 2722 | OE1 | GLU | 533 | A | 3531 | NZ | LYS | 60 | B | 2.6 |
| | 2723 | OE2 | GLU | 533 | A | 3986 | NZ | LYS | 116 | B | 2.62 |
| | 2900 | O | ASP | 555 | A | 3986 | NZ | LYS | 116 | B | 2.71 |
| | 2918 | OD1 | ASN | 557 | A | 3986 | NZ | LYS | 116 | B | 2.7 |
| | 2932 | OE1 | GLN | 559 | A | 4027 | N | SER | 121 | B | 3.1 |
| | 3117 | OH | TYR | 581 | A | 4007 | N | GLU | 119 | B | 3.03 |

**Table S6:** Total number of H-bond involved in the initial structure of NiV glycoprotein /EFNB3 complex. The interface H-bond results obtained from PDBsum server.

| | ATOM 1 (NiV Glycoprotein) | | | | | ATOM 2 (Ephrin B3) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Complex** | **Atom no.** | **Atom name** | **Res name** | **Res no.** | **Chain** | **Atom no.** | **Atom name** | **Res name** | **Res no.** | **Chain** | **Distance** |
| **NiV glycoprotein /EFNB3** | 586 | N | CYS | 240 | A | 5008 | OE1 | GLU | 119 | B | 2.75 |
| | 597 | OG | SER | 241 | A | 5009 | OE2 | GLU | 119 | B | 2.56 |
| | 607 | NE | ARG | 242 | A | 5101 | OE1 | GLU | 128 | B | 2.6 |
| | 613 | NH2 | ARG | 242 | A | 5102 | OE2 | GLU | 128 | B | 2.79 |
| | 2023 | OH | TYR | 389 | A | 5277 | NH1 | ARG | 145 | B | 3.09 |
| | 2023 | OH | TYR | 389 | A | 5280 | NH2 | ARG | 145 | B | 2.75 |
| | 3020 | OG | SER | 491 | A | 4823 | O | LEU | 101 | B | 2.97 |
| | 3402 | NE2 | GLN | 530 | A | 4934 | O | ARG | 112 | B | 3.35 |
| | 3428 | OE1 | GLU | 533 | A | 4405 | NH2 | ARG | 57 | B | 3.09 |
| | 3648 | OD2 | ASP | 555 | A | 4405 | NH2 | ARG | 57 | B | 2.67 |
| | 3665 | OD1 | ASN | 557 | A | 4972 | NZ | LYS | 116 | B | 2.7 |

**Table S7:** Total number of H-bond involved in the initial structure of HeV glycoprotein /EFNB2 complex. The interface H-bond results obtained from PDBsum server.

| | ATOM 1 (HeV Glycoprotein) | | | | | ATOM 2 (Ephrin B2) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Complex** | **Atom no.** | **Atom name** | **Res name** | **Res no.** | **Chain** | **Atom no.** | **Atom name** | **Res name** | **Res no.** | **Chain** | **Distance** |
| **HeV glycoprotein /EFNB2** | 503 | N | CYS | 240 | A | 727 | OE2 | GLU | 116 | B | 3.08 |
| | 524 | NH2 | ARG | 242 | A | 783 | O | TRP | 122 | B | 2.55 |
| | 1677 | NZ | LYS | 388 | A | 629 | OD2 | ASP | 105 | B | 2.22 |
| | 1689 | OH | TYR | 389 | A | 624 | N | ASP | 105 | B | 3.07 |
| | 2484 | OE1 | GLN | 490 | A | 759 | ND2 | ASN | 120 | B | 2.91 |
| | 2611 | N | GLY | 506 | A | 753 | O | PRO | 119 | B | 2.88 |
| | 2808 | NE2 | GLN | 530 | A | 665 | O | LYS | 109 | B | 2.96 |
| | 2822 | O | ALA | 532 | A | 718 | NE2 | GLN | 115 | B | 2.99 |
| | 2828 | OE1 | GLU | 533 | A | 698 | NZ | LYS | 113 | B | 2.59 |
| | 3010 | O | ASP | 555 | A | 698 | NZ | LYS | 113 | B | 2.8 |
| | 3022 | OD1 | ASN | 557 | A | 698 | NZ | LYS | 113 | B | 2.53 |
| | 3219 | OH | TYR | 581 | A | 721 | N | GLU | 116 | B | 3.05 |

**Table S8:** Total number of H-bond involved in the initial structure of HeV glycoprotein /EFNB3 complex. The interface H-bond results obtained from PDBsum server.

| | ATOM 1 (HeV Glycoprotein) | | | | | ATOM 2 (Ephrin B3) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Complex** | **Atom no.** | **Atom name** | **Res name** | **Res no.** | **Chain** | **Atom no.** | **Atom name** | **Res name** | **Res no.** | **Chain** | **Distance** |
| **HeV glycoprotein /EFNB3** | 611 | N | CYS | 240 | A | 5009 | OE2 | GLU | 119 | B | 2.69 |
| | 618 | N | THR | 241 | A | 5009 | OE2 | GLU | 119 | B | 2.66 |
| | 622 | OG1 | THR | 241 | A | 5009 | OE2 | GLU | 119 | B | 2.77 |
| | 633 | NE | ARG | 242 | A | 5101 | OE1 | GLU | 128 | B | 3.22 |
| | 639 | NH2 | ARG | 242 | A | 5101 | OE1 | GLU | 128 | B | 2.57 |
| | 2042 | NZ | LYS | 388 | A | 4887 | OD1 | ASP | 108 | B | 2.67 |
| | 2058 | OH | TYR | 389 | A | 4857 | O | ASP | 105 | B | 2.98 |
| | 2058 | OH | TYR | 389 | A | 5281 | NH2 | ARG | 145 | B | 2.69 |
| | 3151 | OE2 | GLU | 501 | A | 4867 | NH1 | ARG | 106 | B | 2.98 |
| | 3436 | NE2 | GLN | 530 | A | 4934 | O | ARG | 112 | B | 3.08 |
| | 3672 | OD2 | ASP | 555 | A | 4972 | NZ | LYS | 116 | B | 2.54 |
| | 3689 | OD1 | ASN | 557 | A | 4997 | NE2 | GLN | 118 | B | 2.79 |

**Table S9:** Number of salt bridges observed complex of the NiV glycoprotein /EFNB2, NiV glycoprotein /EFNB3, HeV glycoprotein /EFNB2 and HeV glycoprotein /EFNB3 PPI complexes. The salt bridges atom-atom interactions at PPI interface obtained from PDBsum server

| | ATOM 1 (Glycoprotein) | | | | | ATOM 2 (Ephrins) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Complex** | **Atom no.** | **Atom name** | **Res. Name** | **Res. no.** | **Atom Chain** | **Atom no.** | **Atom name** | **Res. Name** | **Res. no.** | **Atom Chain** | **Distance** |
| NiV | 2465 | OE2 | GLU | 501 | A | 3902 | NZ | LYS | 106 | B | 2.59 |
| glycoprotein | 2722 | OE1 | GLU | 533 | A | 3531 | NZ | LYS | 60 | B | 2.60 |
| /EFNB2 | 2723 | OE2 | GLU | 533 | A | 3986 | NZ | LYS | 116 | B | 2.62 |
| NiV | 607 | NE | ARG | 242 | A | 5101 | OE1 | GLU | 128 | B | 2.6 |
| glycoprotein | 3429 | OE2 | GLU | 533 | A | 4405 | NH2 | ARG | 57 | B | 3.09 |
| /EFNB3 | 3429 | OE2 | GLU | 533 | A | 4972 | NZ | LYS | 116 | B | 3.41 |
| | 3648 | OD2 | ASP | 555 | A | 4405 | NH2 | ARG | 57 | B | 2.67 |
| HeV | 1677 | NZ | LYS | 388 | A | 629 | OD2 | ASP | 105 | B | 2.22 |
| glycoprotein | 2571 | OE1 | GLU | 501 | A | 614 | NZ | LYS | 103 | B | 3.87 |
| /EFNB2 | 2829 | OE2 | GLU | 533 | A | 243 | NZ | LYS | 57 | B | 3.39 |
| | 2828 | OE1 | GLU | 533 | A | 698 | NZ | LYS | 113 | B | 2.59 |
| HeV | 639 | NH2 | ARG | 242 | A | 5101 | OE1 | GLU | 128 | B | 2.57 |
| glycoprotein | 2042 | NZ | LYS | 388 | A | 4887 | OD1 | ASP | 108 | B | 2.67 |
| /EFNB3 | 3151 | OE2 | GLU | 501 | A | 4867 | NH1 | ARG | 106 | B | 2.98 |
| | 3462 | OE1 | GLU | 533 | A | 4399 | NE | ARG | 57 | B | 3.86 |
| | 3671 | OD1 | ASP | 555 | A | 4972 | NZ | LYS | 116 | B | 2.54 |

**Table S10:** Total number of H-bond involved in the average conformer of NiV glycoprotein /EFNB2 complex extracted from last 50 ns of 250 ns MD trajectory. The interface H-bond results obtained from PDBsum server.

| | ATOM 1 (NiV Glycoprotein) | | | | | ATOM 2 (Ephrin B2) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Complex** | **Atom no.** | **Atom name** | **Res name** | **Res no.** | **Chain** | **Atom no.** | **Atom name** | **Res name** | **Res no.** | **Chain** | **Distance** |
| **NiV glycoprotein /EFNB2** | 844 | NE | ARG | 242 | A | 8124 | OE2 | GLU | 128 | B | 3.15 |
| | 850 | NH2 | ARG | 242 | A | 8123 | OE1 | GLU | 128 | B | 3.13 |
| | 850 | NH2 | ARG | 242 | A | 8124 | OE2 | GLU | 128 | B | 3.26 |
| | 3123 | OH | TYR | 389 | A | 7783 | OD1 | ASP | 108 | B | 2.89 |
| | 4731 | NE2 | GLN | 490 | A | 7890 | O | THR | 114 | B | 3.10 |
| | 4743 | OG | SER | 491 | A | 7685 | O | LEU | 101 | B | 3.09 |
| | 4758 | OE1 | GLN | 492 | A | 7705 | N | ASN | 103 | B | 3.02 |
| | 4759 | NE2 | GLN | 492 | A | 7718 | O | ASN | 103 | B | 3.14 |
| | 4895 | OE1 | GLU | 501 | A | 7755 | NZ | LYS | 106 | B | 2.73 |
| | 4896 | OE2 | GLU | 501 | A | 7755 | NZ | LYS | 106 | B | 2.81 |
| | 4967 | N | GLY | 506 | A | 8028 | O | PRO | 122 | B | 3.00 |
| | 5353 | O | GLN | 530 | A | 7883 | OG1 | THR | 114 | B | 2.64 |
| | 5349 | NE2 | GLN | 530 | A | 7856 | O | LYS | 112 | B | 3.01 |
| | 5389 | OE1 | GLU | 533 | A | 7008 | NZ | LYS | 60 | B | 2.79 |
| | 5746 | O | ASP | 555 | A | 7926 | NZ | LYS | 116 | B | 2.90 |
| | 5769 | OD1 | ASN | 557 | A | 7926 | NZ | LYS | 116 | B | 2.79 |

**Table S11:** Total number of H-bond involved in the average conformer of NiV glycoprotein /EFNB3 complex extracted from last 50 ns of 250 ns MD trajectory. The interface H-bond results obtained from PDBsum server.

| | ATOM 1 (NiV Glycoprotein) | | | | | ATOM 2 (Ephrin B3) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Complex** | **Atom no.** | **Atom name** | **Res name** | **Res no.** | **Chain** | **Atom no.** | **Atom name** | **Res name** | **Res no.** | **Chain** | **Distance** |
| **NiV glycoprotein /EFNB3** | 972 | OG | SER | 239 | A | 8137 | OE1 | GLU | 119 | B | 2.84 |
| | 5133 | N | GLY | 506 | A | 8186 | O | PRO | 122 | B | 2.97 |
| | 5555 | OE1 | GLU | 533 | A | 7146 | NH1 | ARG | 57 | B | 3.28 |
| | 5556 | OE2 | GLU | 533 | A | 7146 | NH1 | ARG | 57 | B | 3.10 |
| | 5935 | OD1 | ASN | 557 | A | 8083 | NZ | LYS | 116 | B | 2.85 |

**Table S12:** Total number of H-bond involved in the average conformer of HeV glycoprotein /EFNB2 complex extracted from last 50 ns of 250 ns MD trajectory. The interface H-bond results obtained from PDBsum server.

| | ATOM 1 (HeV Glycoprotein) | | | | | ATOM 2 (Ephrin B2) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Complex** | **Atom no.** | **Atom name** | **Res name** | **Res no.** | **Chain** | **Atom no.** | **Atom name** | **Res name** | **Res no.** | **Chain** | **Distance** |
| **HeV glycoprotein /EFNB2** | 1021 | OG | SER | 239 | A | 8311 | OE1 | GLU | 125 | B | 2.58 |
| | 1021 | OG | SER | 239 | A | 8312 | OE2 | GLU | 125 | B | 2.70 |
| | 1041 | OG1 | THR | 241 | A | 8311 | OE1 | GLU | 125 | B | 2.89 |
| | 4972 | OG | SER | 491 | A | 7873 | O | LEU | 98 | B | 2.81 |
| | 5126 | OE1 | GLU | 501 | A | 7943 | NZ | LYS | 103 | B | 2.66 |
| | 5127 | OE2 | GLU | 501 | A | 7943 | NZ | LYS | 103 | B | 2.74 |
| | 5195 | N | GLY | 506 | A | 8216 | O | PRO | 119 | B | 3.20 |
| | 5575 | NE2 | GLN | 530 | A | 8044 | O | LYS | 109 | B | 3.13 |
| | 5615 | OE1 | GLU | 533 | A | 8114 | NZ | LYS | 113 | B | 3.04 |
| | 5965 | O | ASP | 555 | A | 8114 | NZ | LYS | 113 | B | 3.06 |
| | 6380 | OH | TYR | 581 | A | 8168 | OE1 | GLU | 116 | B | 3.18 |

**Table S13:** Total number of H-bond involved in the average conformer of HeV glycoprotein /EFNB3 complex extracted from last 50 ns of 250 ns MD trajectory. The interface H-bond results obtained from PDBsum server.

| | ATOM 1 (HeV Glycoprotein) | | | | | ATOM 2 (Ephrin B3) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Complex** | **Atom no.** | **Atom name** | **Res name** | **Res no.** | **Chain** | **Atom no.** | **Atom name** | **Res name** | **Res no.** | **Chain** | **Distance** |
| **HeV glycoprotein /EFNB3** | 1020 | OG | SER | 239 | A | 8153 | OE1 | GLU | 119 | B | 3.16 |
| | 1024 | N | CYS | 240 | A | 8154 | OE2 | GLU | 119 | B | 3.35 |
| | 1067 | NH2 | ARG | 242 | A | 8298 | O | GLU | 128 | B | 2.81 |
| | 4958 | OE1 | GLN | 490 | A | 8185 | OG | SER | 121 | B | 2.81 |
| | 4971 | OG | SER | 491 | A | 7813 | N | LEU | 100 | B | 2.97 |
| | 5602 | O | ALA | 532 | A | 8137 | NE2 | GLN | 118 | B | 3.19 |
| | 5615 | OE2 | GLU | 533 | A | 8099 | NZ | LYS | 116 | B | 2.91 |

**Table S14:** Number of salt bridges observed in the average 50 ns conformer of the NiV G/EFNB2, NiV glycoprotein /EFNB3, HeV glycoprotein /EFNB2 and HeV glycoprotein /EFNB3 PPI complexes. The salt bridges atom-atom interactions at PPI interface obtained from PDBsum server

| **ATOM 1 (Glycoprotein)** | | | | | | **ATOM 2 (Ephrins)** | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Complex** | **Atom no.** | **Atom name** | **Res. Name** | **Res. no.** | **Atom Chain** | **Atom no.** | **Atom name** | **Res. Name** | **Res. no.** | **Atom Chain** | **Distance** |
| NiV glycoprotein /EFNB2 | 850 | NH2 | ARG | 242 | A | 8123 | OE1 | GLU | 128 | B | 3.13 |
| | 4895 | OE1 | GLU | 501 | A | 7755 | NZ | LYS | 106 | B | 2.73 |
| | 5389 | OE1 | GLU | 533 | A | 7008 | NZ | LYS | 60 | B | 2.79 |
| | 5390 | OE2 | GLU | 533 | A | 7926 | NZ | LYS | 116 | B | 3.36 |
| NiV glycoprotein /EFNB3 | 5556 | OE2 | GLU | 533 | A | 7146 | NH1 | ARG | 57 | B | 3.10 |
| HeV glycoprotein /EFNB2 | 5126 | OE1 | GLU | 501 | A | 7943 | NZ | LYS | 103 | B | 2.66 |
| | 5615 | OE1 | GLU | 533 | A | 8114 | NZ | LYS | 113 | B | 3.04 |
| HeV glycoprotein /EFNB3 | 5126 | OE2 | GLU | 533 | Aa | 7146 | NH1 | ARG | 57 | B | 3.10 |