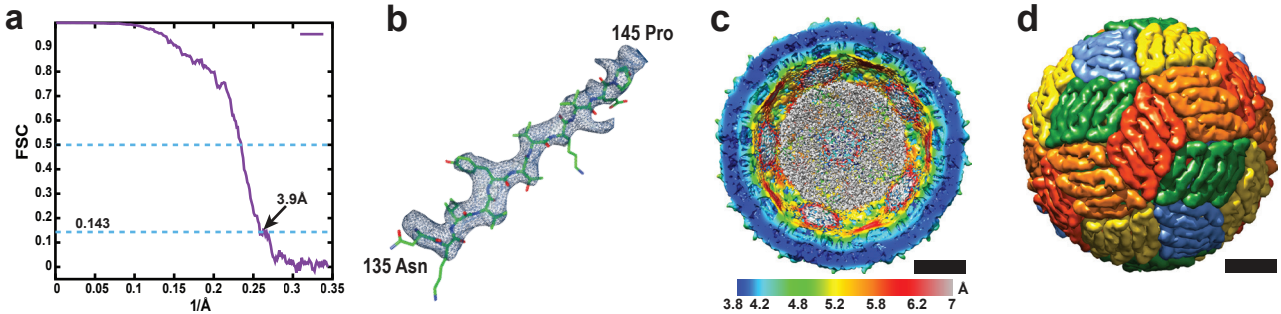
# Supplementary information

# Structure of tick-borne encephalitis virus and its neutralization by a monoclonal antibody

**Füzik et al.**




**Supplementary Figure 1. Cryo-EM reconstruction of TBEV virion.** (a) Fourier shell correlation curve of final reconstruction of TBEV virion calculated according to "gold standard". (b) Example electron density map of E-protein with corresponding structure. (c) Local resolution of cryo-EM map of TBEV virion. The display shows a cut-away half map colored according to the local resolution. The best resolved rigid parts include the ectodomains of the E-proteins. In contrast the virus membrane was reconstructed with less detail. Parts of the map with resolution worse than 7 Å are shown in grey. The non-sharpened electron density map was used for the display. (d) Molecular surface of TBEV virion low-pass filtered to 20 Å to show "Herringbone" organization of envelope proteins. Three dimers of E-proteins form a "raft" that is characteristic for flaviviruses. Scale bars in (c) and (d) represent 10 nm.

## E-protein A - A2 interfaces

**Hydrogen bonds**

| ## | Structure 1 | Dist. [Å] | Structure 2 |
|---|---|---|---|
| 1 | A2:GLU 387[ OE1] | 3.57 | A:LYS 309[ NZ ] |

**Salt bridges**

| ## | Structure 1 | Dist. [Å] | Structure 2 |
|---|---|---|---|
| 1 | A2:GLU 387[ OE1] | 3.57 | A:LYS 309[ NZ ] |

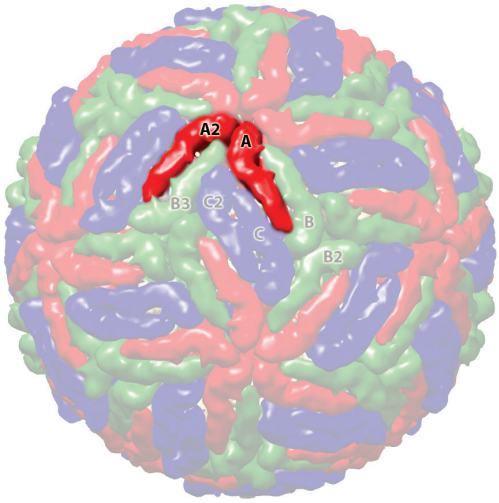
Interface area: 420 Å²

**Interfacing residues**

Inaccessible residues
Solvent-accessible residues
HSDC Residues making **H**ydrogen/**D**isulphide bond, **S**alt bridge or **C**ovalent link
Interfacing residues
**ASA** Accessible Surface Area, Å² **BSA** Buried Surface Area, Å² **ΔG** Solvation energy effect, kcal/mol |||| Buried area percentage, one bar per 10%

| ## | Structure 1 | HSDC | ASA | BSA | ΔG |
|---|---|---|---|---|---|
| 310 | A2:THR 310 | | 92.39 | 13.41 \|\| | 0.03 |
| 311 | A2:LYS 311 | | 90.90 | 0.75 \| | 0.01 |
| 312 | A2:PHE 312 | | 6.25 | 4.41 \|\|\|\|\|\|\| | -0.05 |
| 313 | A2:THR 313 | | 81.35 | 65.64 \|\|\|\|\|\|\|\| | 0.99 |
| 314 | A2:TRP 314 | | 63.31 | 60.74 \|\|\|\|\|\|\|\|\| | 0.20 |
| 315 | A2:LYS 315 | | 134.73 | 12.48 \| | 0.05 |
| 317 | A2:ALA 317 | | 60.75 | 23.29 \|\|\|\| | 0.35 |
| 319 | A2:THR 319 | | 68.29 | 1.47 \| | -0.02 |
| 333 | A2:SER 333 | | 86.20 | 1.73 \| | -0.01 |
| 347 | A2:HIS 347 | | 106.13 | 59.61 \|\|\|\|\| | 0.46 |
| 348 | A2:GLY 348 | | 62.96 | 12.87 \|\|\| | 0.18 |
| 349 | A2:SER 349 | | 116.52 | 44.25 \|\|\|\| | 0.43 |
| 350 | A2:PRO 350 | | 40.31 | 9.02 \|\|\| | 0.14 |
| 387 | A2:GLU 387 | HS | 116.75 | 34.98 \|\|\| | 0.03 |
| 388 | A2:LEU 388 | | 40.33 | 38.58 \|\|\|\|\|\|\|\| | 0.62 |
| 389 | A2:SER 389 | | 54.64 | 3.40 \| | -0.04 |
| 390 | A2:HIS 390 | | 62.88 | 6.38 \|\| | -0.03 |
| 391 | A2:GLN 391 | | 121.61 | 24.42 \|\|\| | -0.27 |
| 395 | A2:LYS 395 | | 139.92 | 10.30 \| | -0.08 |

| ## | Structure 2 | HSDC | ASA | BSA | ΔG |
|---|---|---|---|---|---|
| 16 | A:GLN 16 | | 144.39 | 11.95 \| | 0.15 |
| 302 | A:LEU 302 | | 100.55 | 50.75 \|\|\|\|\| | 0.43 |
| 303 | A:THR 303 | | 134.11 | 44.75 \|\|\|\| | 0.36 |
| 304 | A:TYR 304 | | 57.44 | 3.33 \| | -0.02 |
| 305 | A:THR 305 | | 96.64 | 26.15 \|\|\| | 0.42 |
| 306 | A:MET 306 | | 98.65 | 46.64 \|\|\|\|\| | 0.69 |
| 309 | A:LYS 309 | HS | 114.39 | 30.84 \|\|\| | -1.05 |
| 339 | A:ARG 339 | | 67.64 | 50.60 \|\|\|\|\|\|\| | -1.12 |
| 349 | A:SER 349 | | 116.52 | 10.80 \| | -0.12 |
| 350 | A:PRO 350 | | 40.31 | 6.12 \|\| | -0.05 |
| 351 | A:ASP 351 | | 144.98 | 31.67 \|\|\| | 0.05 |
| 352 | A:VAL 352 | | 93.60 | 56.65 \|\|\|\|\|\| | 0.91 |
| 353 | A:ASN 353 | | 78.79 | 38.18 \|\|\|\| | -0.07 |




## E-protein B - B2 interfaces

**Hydrogen bonds**

| ## | Structure 1 | Dist. [Å] | Structure 2 |
|---|---|---|---|
| 1 | B2:SER 168[ N ] | 2.93 | B:ASP 351[ O ] |
| 2 | B2:ASN 135[ OD1] | 2.07 | B:ASP 351[ N ] |
| 3 | B2:GLU 295[ OE2] | 3.79 | B:GLN 16[ NE2] |

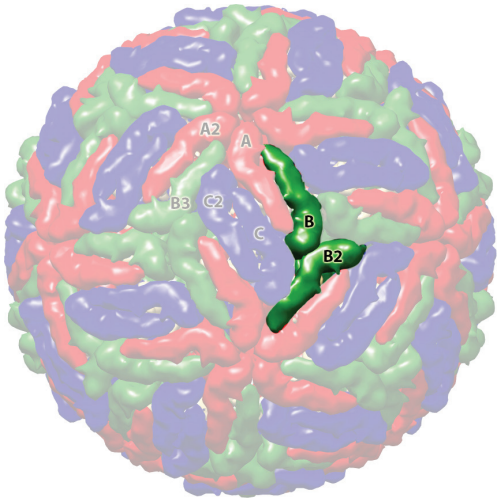
Interface area: 410 Å²

**Interfacing residues**

Inaccessible residues
Solvent-accessible residues
HSDC Residues making **H**ydrogen/**D**isulphide bond, **S**alt bridge or **C**ovalent link
Interfacing residues
**ASA** Accessible Surface Area, Å² **BSA** Buried Surface Area, Å² **ΔG** Solvation energy effect, kcal/mol |||| Buried area percentage, one bar per 10%

| ## | Structure 1 | HSDC | ASA | BSA | ΔG |
|---|---|---|---|---|---|
| 19 | B2:THR 19 | | 48.51 | 6.19 \|\| | 0.10 |
| 20 | B2:ARG 20 | | 115.47 | 46.75 \|\|\|\|\| | -0.04 |
| 134 | B2:ALA 134 | | 53.07 | 1.34 \| | 0.02 |
| 135 | B2:ASN 135 | H | 105.24 | 58.71 \|\|\|\|\|\| | -0.54 |
| 167 | B2:VAL 167 | | 69.50 | 56.09 \|\|\|\|\|\|\| | 0.57 |
| 168 | B2:SER 168 | H | 95.27 | 50.21 \|\|\|\|\| | 0.65 |
| 170 | B2:GLU 170 | | 86.98 | 25.78 \|\|\| | -0.29 |
| 172 | B2:THR 172 | | 50.35 | 4.18 \| | 0.07 |
| 173 | B2:ILE 173 | | 107.75 | 55.78 \|\|\|\|\|\| | 0.78 |
| 175 | B2:THR 175 | | 93.85 | 8.52 \| | -0.09 |
| 181 | B2:ASP 181 | | 44.88 | 7.98 \|\| | -0.14 |
| 189 | B2:ALA 189 | | 95.69 | 11.55 \|\| | 0.18 |
| 295 | B2:GLU 295 | H | 95.83 | 11.78 \|\| | -0.12 |
| 296 | B2:LYS 296 | | 134.29 | 24.77 \|\| | -0.42 |

| ## | Structure 2 | HSDC | ASA | BSA | ΔG |
|---|---|---|---|---|---|
| 16 | B:GLN 16 | H | 154.11 | 87.11 \|\|\|\|\| | -0.15 |
| 37 | B:GLY 37 | | 50.45 | 4.51 \| | -0.04 |
| 38 | B:LYS 38 | | 52.11 | 0.65 \| | 0.01 |
| 297 | B:LEU 297 | | 11.71 | 3.93 \|\|\| | -0.04 |
| 298 | B:LYS 298 | | 124.19 | 9.20 \| | 0.15 |
| 302 | B:LEU 302 | | 103.21 | 47.31 \|\|\|\| | 0.57 |
| 303 | B:THR 303 | | 134.07 | 15.90 \|\| | 0.25 |
| 339 | B:ARG 339 | | 69.62 | 14.99 \|\|\| | -0.50 |
| 343 | B:ARG 343 | | 102.14 | 33.67 \|\|\| | 0.21 |
| 345 | B:VAL 345 | | 8.21 | 0.67 \| | 0.01 |
| 350 | B:PRO 350 | | 84.30 | 22.18 \|\|\| | 0.34 |
| 351 | B:ASP 351 | H | 144.19 | 138.85 \|\|\|\|\|\|\|\| | -0.59 |
| 352 | B:VAL 352 | | 76.68 | 29.46 \|\|\|\| | 0.47 |
| 353 | B:ASN 353 | | 76.29 | 37.36 \|\|\|\| | 0.14 |




## E-protein A - B3 interfaces

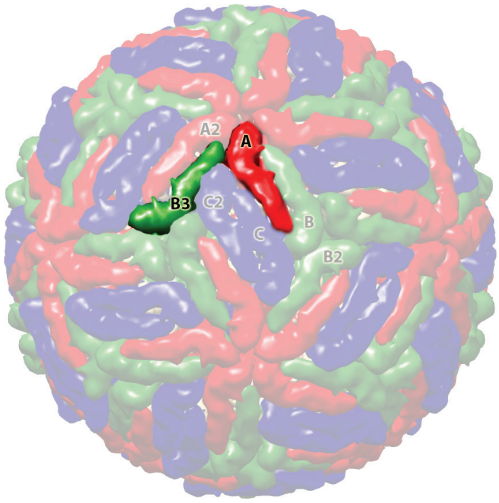
Interface area: 235 Å²

**Interfacing residues**

Inaccessible residues
Solvent-accessible residues
HSDC Residues making **H**ydrogen/**D**isulphide bond, **S**alt bridge or **C**ovalent link
Interfacing residues
**ASA** Accessible Surface Area, Å² **BSA** Buried Surface Area, Å² **ΔG** Solvation energy effect, kcal/mol |||| Buried area percentage, one bar per 10%

| ## | Structure 1 | HSDC | ASA | BSA | ΔG |
|---|---|---|---|---|---|
| 73 | B3:ARG 73 | | 101.91 | 20.38 \|\| | -0.06 |
| 76 | B3:THR 76 | | 96.76 | 77.09 \|\|\|\|\|\|\| | 0.61 |
| 77 | B3:MET 77 | | 123.35 | 69.98 \|\|\|\|\|\| | 1.50 |
| 78 | B3:GLY 78 | | 40.36 | 25.63 \|\|\|\|\|\| | 0.23 |
| 79 | B3:PRO 79 | | 92.16 | 6.36 \| | 0.10 |
| 107 | B3:LEU 107 | | 107.17 | 38.50 \|\|\|\| | 0.62 |

| ## | Structure 2 | HSDC | ASA | BSA | ΔG |
|---|---|---|---|---|---|
| 16 | A:GLN 16 | | 144.39 | 44.86 \|\|\|\| | -0.39 |
| 17 | A:GLY 17 | | 67.94 | 20.37 \|\|\| | 0.18 |
| 19 | A:THR 19 | | 44.66 | 27.64 \|\|\|\|\|\| | 0.44 |
| 20 | A:ARG 20 | | 102.77 | 4.52 \| | 0.07 |
| 38 | A:LYS 38 | | 43.45 | 18.44 \|\|\|\| | -0.43 |
| 295 | A:GLU 295 | | 82.96 | 70.35 \|\|\|\|\|\|\|\| | 0.33 |
| 296 | A:LYS 296 | | 127.50 | 43.50 \|\|\|\| | -0.62 |
| 297 | A:LEU 297 | | 11.61 | 0.86 \| | -0.01 |




**Supplementary Figure 2. Non-quasi equivalent E-protein interfaces in TBEV particle.** The tables show hydrogen bonds, salt bridges and interfacing amino acids with buried surfaces participating in E-protein interactions. The interfaces are shown on the TBEV particles on the right side of the figure. Figure continued on next page.....

## E-protein A - C2 interfaces

**Hydrogen bonds**

| ## | Structure 1 | Dist. [A] | Structure 2 |
|---|---|---|---|
| 1 | C2:GLN 391[ N ] | 2.51 | A:VAL 167[ O ] |
| 2 | C2:GLN 391[ NE2] | 2.97 | A:SER 169[ O ] |
| 3 | C2:ASP 380[ OD2] | 3.52 | A:SER 190[ OG ] |

**Salt bridges**

| ## | Structure 1 | Dist. [A] | Structure 2 |
|---|---|---|---|
| 1 | C2:HIS 347[ NE2] | 3.21 | A:GLU 291[ OE1] |
| 2 | C2:HIS 347[ ND1] | 3.71 | A:GLU 291[ OE2] |
| 3 | C2:HIS 347[ NE2] | 2.64 | A:GLU 291[ OE2] |
| 4 | C2:ASP 380[ OD2] | 3.73 | A:ARG 187[ NE ] |

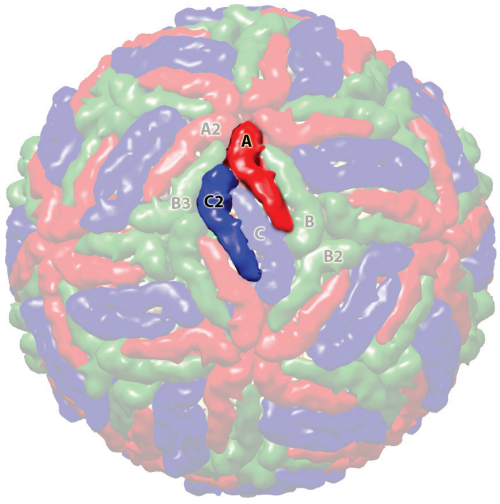
Interface area: 470 Å²

**Interfacing residues**

Inaccessible residues
Solvent-accessible residues
HSDC Residues making **H**ydrogen/**D**isulphide bond, **S**alt bridge or **C**ovalent link
Interfacing residues
**ASA** Accessible Surface Area, Å² **BSA** Buried Surface Area, Å² **ΔG** Solvation energy effect, kcal/mol |||| Buried area percentage, one bar per 10%

| ## | Structure 1 | HSDC | ASA | BSA | ΔG |
|---|---|---|---|---|---|
| 314 | C2:TRP 314 | | 65.08 | 5.58 \| | 0.01 |
| 317 | C2:ALA 317 | | 60.00 | 13.56 \|\|\| | 0.22 |
| 318 | C2:PRO 318 | | 8.71 | 8.22 \|\|\|\|\|\|\|\|\| | -0.09 |
| 319 | C2:THR 319 | | 61.24 | 3.68 \| | 0.06 |
| 347 | C2:HIS 347 | S | 149.57 | 80.08 \|\|\|\|\| | 0.60 |
| 380 | C2:ASP 380 | HS | 84.95 | 52.29 \|\|\|\|\|\| | -0.39 |
| 382 | C2:ILE 382 | | 26.60 | 16.55 \|\|\|\|\|\| | 0.26 |
| 384 | C2:TYR 384 | | 56.91 | 24.19 \|\|\|\|\| | 0.08 |
| 387 | C2:GLU 387 | | 116.52 | 11.10 \| | -0.09 |
| 388 | C2:LEU 388 | | 40.07 | 1.34 \| | 0.02 |
| 389 | C2:SER 389 | | 55.80 | 47.80 \|\|\|\|\|\|\| | -0.38 |
| 390 | C2:HIS 390 | | 59.88 | 52.88 \|\|\|\|\|\|\| | -0.12 |
| 391 | C2:GLN 391 | H | 129.68 | 121.96 \|\|\|\|\|\|\|\|\| | 0.15 |
| 392 | C2:TRP 392 | | 34.38 | 5.94 \|\| | 0.07 |
| 393 | C2:PHE 393 | | 127.41 | 29.08 \|\|\| | 0.42 |

| ## | Structure 2 | HSDC | ASA | BSA | ΔG |
|---|---|---|---|---|---|
| 135 | A:ASN 135 | | 102.88 | 38.05 \|\|\|\| | -0.25 |
| 166 | A:THR 166 | | 38.97 | 0.37 \| | -0.00 |
| 167 | A:VAL 167 | H | 83.73 | 70.48 \|\|\|\|\|\|\|\| | 0.58 |
| 168 | A:SER 168 | | 104.25 | 44.79 \|\|\|\|\| | 0.54 |
| 169 | A:SER 169 | H | 36.75 | 11.32 \|\|\| | -0.10 |
| 170 | A:GLU 170 | | 144.22 | 87.14 \|\|\|\|\|\| | 0.06 |
| 185 | A:LEU 185 | | 51.30 | 21.23 \|\|\|\| | 0.34 |
| 186 | A:CYS 186 | | 8.81 | 8.23 \|\|\|\|\|\|\|\| | -0.09 |
| 187 | A:ARG 187 | S | 104.97 | 90.72 \|\|\|\|\|\|\|\| | -0.40 |
| 188 | A:VAL 188 | | 10.42 | 7.09 \|\|\|\|\|\| | 0.00 |
| 189 | A:ALA 189 | | 100.01 | 57.20 \|\|\|\|\|\| | 0.82 |
| 190 | A:SER 190 | H | 42.16 | 17.50 \|\|\|\|\| | 0.27 |
| 291 | A:GLU 291 | S | 28.77 | 9.82 \|\|\|\| | -0.15 |




## E-protein C - C2 interfaces

**Hydrogen bonds**

| ## | Structure 1 | Dist. [A] | Structure 2 |
|---|---|---|---|
| 1 | C2:GLY 102[ N ] | 3.18 | C:TYR 150[ OH ] |
| 2 | C2:HIS 208[ ND1] | 3.70 | C:VAL 254[ O ] |
| 3 | C2:HIS 208[ NE2] | 3.22 | C:LEU 65[ O ] |
| 4 | C2:ASN 256[ N ] | 2.63 | C:HIS 208[ O ] |
| 5 | C2:LYS 266[ NZ ] | 2.49 | C:GLN 260[ OE1] |
| 6 | C2:TYR 150[ OH ] | 3.18 | C:GLY 102[ N ] |
| 7 | C2:VAL 254[ O ] | 3.70 | C:HIS 208[ ND1] |
| 8 | C2:LEU 65[ O ] | 3.22 | C:HIS 208[ NE2] |
| 9 | C2:HIS 208[ O ] | 2.63 | C:ASN 256[ N ] |
| 10 | C2:GLN 260[ OE1] | 2.49 | C:LYS 266[ NZ ] |

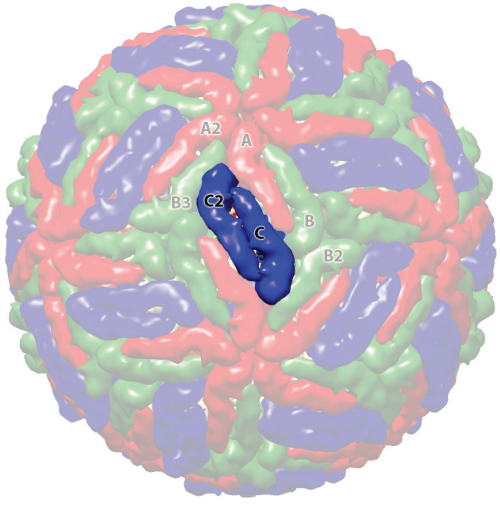
Interface area: 1570 Å²

**Interfacing residues**

Inaccessible residues
Solvent-accessible residues
HSDC Residues making **H**ydrogen/**D**isulphide bond, **S**alt bridge or **C**ovalent link
Interfacing residues
**ASA** Accessible Surface Area, Å² **BSA** Buried Surface Area, Å² **ΔG** Solvation energy effect, kcal/mol |||| Buried area percentage, one bar per 10%

| ## | Structure 1 | HSDC | ASA | BSA | ΔG |
|---|---|---|---|---|---|
| 4 | C2:THR 4 | | 29.46 | 22.95 \|\|\|\|\|\|\| | -0.06 |
| 5 | C2:HIS 5 | | 64.51 | 23.19 \|\|\|\| | 0.02 |
| 7 | C2:GLU 7 | | 159.27 | 34.61 \|\|\| | 0.06 |
| 62 | C2:HIS 62 | | 51.27 | 8.13 \|\| | 0.13 |
| 65 | C2:LEU 65 | H | 45.97 | 29.64 \|\|\|\|\|\| | 0.15 |
| 66 | C2:SER 66 | | 54.34 | 5.52 \|\| | 0.09 |
| 67 | C2:ASP 67 | | 85.01 | 0.14 \| | -0.00 |
| 68 | C2:THR 68 | | 78.34 | 17.64 \|\|\| | -0.20 |
| 98 | C2:ASP 98 | | 93.78 | 41.72 \|\|\|\|\| | -0.24 |
| 100 | C2:GLY 100 | | 16.74 | 13.23 \|\|\|\|\|\|\| | 0.21 |
| 101 | C2:TRP 101 | | 167.93 | 132.06 \|\|\|\|\|\|\|\|\|\|\|\|\|\|\| | 1.51 |
| 102 | C2:GLY 102 | H | 72.84 | 69.19 \|\|\|\|\|\|\|\|\| | 0.52 |
| 103 | C2:ASN 103 | | 29.57 | 2.14 \| | -0.00 |
| 104 | C2:HIS 104 | | 161.67 | 37.00 \|\|\| | -0.11 |
| 106 | C2:GLY 106 | | 54.47 | 5.40 \| | -0.06 |
| 107 | C2:LEU 107 | | 104.44 | 21.41 \|\|\| | 0.34 |
| 108 | C2:PHE 108 | | 137.30 | 106.92 \|\|\|\|\|\|\|\|\|\|\|\|\| | 1.61 |
| 110 | C2:LYS 110 | | 101.89 | 1.96 \| | -0.01 |
| 117 | C2:VAL 117 | | 2.26 | 0.84 \|\|\| | 0.01 |
| 125 | C2:LYS 125 | | 67.49 | 9.60 \|\| | -0.36 |
| 150 | C2:TYR 150 | H | 79.73 | 35.44 \|\|\|\|\| | 0.02 |
| 152 | C2:ALA 152 | | 46.09 | 34.81 \|\|\|\|\|\|\| | 0.56 |
| 153 | C2:ALA 153 | | 83.36 | 16.65 \|\| | 0.16 |
| 154 | C2:ASN 154 | | 134.90 | 19.33 \|\| | -0.13 |
| 155 | C2:GLU 155 | | 104.11 | 1.56 \| | 0.02 |
| 206 | C2:VAL 206 | | 67.32 | 4.85 \| | 0.08 |
| 207 | C2:GLU 207 | | 145.95 | 2.21 \| | -0.03 |
| 208 | C2:HIS 208 | H | 163.42 | 144.51 \|\|\|\|\|\|\|\|\| | 0.39 |
| 209 | C2:LEU 209 | | 55.06 | 29.22 \|\|\|\|\| | 0.45 |
| 210 | C2:PRO 210 | | 59.48 | 33.09 \|\|\|\|\| | 0.53 |
| 225 | C2:LEU 225 | | 27.25 | 4.02 \|\| | 0.06 |
| 241 | C2:LEU 241 | | 2.01 | 0.84 \|\|\|\| | 0.01 |
| 254 | C2:VAL 254 | H | 32.62 | 22.83 \|\|\|\|\|\|\| | -0.15 |
| 255 | C2:TYR 255 | | 114.63 | 64.91 \|\|\|\|\|\| | 0.84 |
| 256 | C2:ASN 256 | H | 59.13 | 46.64 \|\|\|\|\|\|\| | -0.05 |
| 257 | C2:LEU 257 | | 83.65 | 49.54 \|\|\|\|\| | 0.48 |
| 258 | C2:GLY 258 | | 24.08 | 18.73 \|\|\|\|\|\|\| | 0.30 |
| 259 | C2:ASP 259 | | 60.98 | 56.80 \|\|\|\|\|\|\|\| | -0.06 |
| 260 | C2:GLN 260 | H | 33.63 | 28.56 \|\|\|\|\|\|\|\| | -0.33 |
| 261 | C2:THR 261 | | 26.31 | 12.38 \|\|\|\| | 0.20 |
| 262 | C2:GLY 262 | | 44.24 | 43.07 \|\|\|\|\|\|\|\|\| | 0.48 |
| 263 | C2:VAL 263 | | 97.65 | 47.52 \|\|\|\|\| | 0.76 |
| 265 | C2:LEU 265 | | 59.16 | 36.75 \|\|\|\|\|\| | 0.56 |
| 266 | C2:LYS 266 | H | 173.11 | 71.14 \|\|\|\|\| | -0.53 |
| 273 | C2:VAL 273 | | 68.14 | 4.35 \| | 0.07 |
| 316 | C2:ARG 316 | | 81.38 | 66.63 \|\|\|\|\|\|\| | -2.36 |
| 317 | C2:ALA 317 | | 60.00 | 0.12 \| | -0.00 |
| 319 | C2:THR 319 | | 61.24 | 43.72 \|\|\|\|\|\|\| | 0.17 |
| 320 | C2:ASP 320 | | 48.78 | 18.40 \|\|\|\| | -0.11 |
| 321 | C2:SER 321 | | 26.59 | 22.22 \|\|\|\|\|\|\| | 0.13 |
| 322 | C2:GLY 322 | | 66.83 | 6.81 \|\| | 0.04 |
| 327 | C2:VAL 327 | | 6.02 | 4.60 \|\|\|\|\| | 0.07 |
| 329 | C2:GLU 329 | | 37.68 | 1.35 \| | -0.02 |

| ## | Structure 2 | HSDC | ASA | BSA | ΔG |
|---|---|---|---|---|---|
| 4 | C:THR 4 | | 29.46 | 23.44 \|\|\|\|\|\|\| | -0.07 |
| 5 | C:HIS 5 | | 64.51 | 23.46 \|\|\|\| | 0.03 |
| 7 | C:GLU 7 | | 159.27 | 34.45 \|\|\| | 0.05 |
| 62 | C:HIS 62 | | 51.27 | 8.44 \|\| | 0.14 |
| 65 | C:LEU 65 | H | 45.97 | 30.30 \|\|\|\|\|\| | 0.14 |
| 66 | C:SER 66 | | 54.34 | 5.69 \|\| | 0.09 |
| 67 | C:ASP 67 | | 85.01 | 0.29 \| | -0.00 |
| 68 | C:THR 68 | | 78.34 | 17.39 \|\|\| | -0.20 |
| 98 | C:ASP 98 | | 93.78 | 42.19 \|\|\|\|\| | -0.25 |
| 100 | C:GLY 100 | | 16.74 | 13.39 \|\|\|\|\|\|\| | 0.21 |
| 101 | C:TRP 101 | | 167.93 | 131.12 \|\|\|\|\|\|\|\|\|\|\|\|\|\| | 1.51 |
| 102 | C:GLY 102 | H | 72.84 | 68.41 \|\|\|\|\|\|\|\|\| | 0.51 |
| 103 | C:ASN 103 | | 29.57 | 1.84 \| | -0.00 |
| 104 | C:HIS 104 | | 161.67 | 37.10 \|\|\| | -0.11 |
| 106 | C:GLY 106 | | 54.47 | 5.60 \|\| | -0.06 |
| 107 | C:LEU 107 | | 104.44 | 22.41 \|\|\| | 0.36 |
| 108 | C:PHE 108 | | 137.30 | 106.68 \|\|\|\|\|\|\| | 1.60 |
| 110 | C:LYS 110 | | 101.89 | 1.89 \| | -0.03 |
| 117 | C:VAL 117 | | 2.26 | 0.67 \|\|\| | 0.01 |
| 125 | C:LYS 125 | | 67.49 | 9.08 \|\| | -0.34 |
| 150 | C:TYR 150 | H | 79.73 | 36.28 \|\|\|\|\| | 0.03 |
| 152 | C:ALA 152 | | 46.09 | 34.51 \|\|\|\|\|\|\| | 0.55 |
| 153 | C:ALA 153 | | 83.36 | 17.30 \|\|\| | 0.17 |
| 154 | C:ASN 154 | | 134.90 | 19.83 \|\| | -0.14 |
| 155 | C:GLU 155 | | 104.11 | 1.24 \| | 0.02 |
| 206 | C:VAL 206 | | 67.32 | 4.69 \| | 0.08 |
| 207 | C:GLU 207 | | 145.95 | 2.95 \| | -0.03 |
| 208 | C:HIS 208 | H | 163.42 | 143.38 \|\|\|\|\|\|\|\| | 0.35 |
| 209 | C:LEU 209 | | 55.06 | 28.26 \|\|\|\|\| | 0.44 |
| 210 | C:PRO 210 | | 59.48 | 32.56 \|\|\|\|\| | 0.51 |
| 225 | C:LEU 225 | | 27.25 | 3.43 \|\| | 0.05 |
| 241 | C:LEU 241 | | 2.01 | 1.00 \|\|\|\| | 0.02 |
| 254 | C:VAL 254 | H | 32.62 | 23.20 \|\|\|\|\|\|\| | -0.15 |
| 255 | C:TYR 255 | | 114.63 | 65.62 \|\|\|\|\|\| | 0.84 |
| 256 | C:ASN 256 | H | 59.13 | 45.83 \|\|\|\|\|\|\| | -0.05 |
| 257 | C:LEU 257 | | 83.65 | 50.87 \|\|\|\|\|\| | 0.51 |
| 258 | C:GLY 258 | | 24.08 | 18.72 \|\|\|\|\|\|\| | 0.30 |
| 259 | C:ASP 259 | | 60.98 | 56.18 \|\|\|\|\|\|\|\| | -0.07 |
| 260 | C:GLN 260 | H | 33.63 | 23.07 \|\|\|\|\|\| | -0.26 |
| 261 | C:THR 261 | | 26.31 | 12.04 \|\|\|\| | 0.19 |
| 262 | C:GLY 262 | | 44.24 | 43.50 \|\|\|\|\|\|\|\| | 0.47 |
| 263 | C:VAL 263 | | 97.65 | 49.05 \|\|\|\|\|\| | 0.78 |
| 265 | C:LEU 265 | | 59.16 | 36.28 \|\|\|\|\|\| | 0.55 |
| 266 | C:LYS 266 | H | 173.11 | 71.43 \|\|\|\|\| | -0.53 |
| 273 | C:VAL 273 | | 68.14 | 5.19 \| | 0.08 |
| 316 | C:ARG 316 | | 81.38 | 67.16 \|\|\|\|\|\|\| | -2.34 |
| 319 | C:THR 319 | | 61.24 | 44.58 \|\|\|\|\|\|\| | 0.19 |
| 320 | C:ASP 320 | | 48.78 | 18.15 \|\|\|\| | -0.12 |
| 321 | C:SER 321 | | 26.59 | 21.54 \|\|\|\|\|\|\| | 0.13 |
| 322 | C:GLY 322 | | 66.83 | 7.46 \|\| | 0.05 |
| 327 | C:VAL 327 | | 6.02 | 5.18 \|\|\|\|\|\| | 0.08 |
| 329 | C:GLU 329 | | 37.68 | 1.47 \| | -0.02 |




**Supplementary Figure 2 (continued). Non-quasi equivalent E-protein interfaces in TBEV particle.** The tables show hydrogen bonds, salt bridges and interfacing amino acids with buried surfaces participating in E-protein interactions. The interfaces are shown on the TBEV particles on the right side of the figure. Figure continued on next page.....

## E-protein A - C interfaces

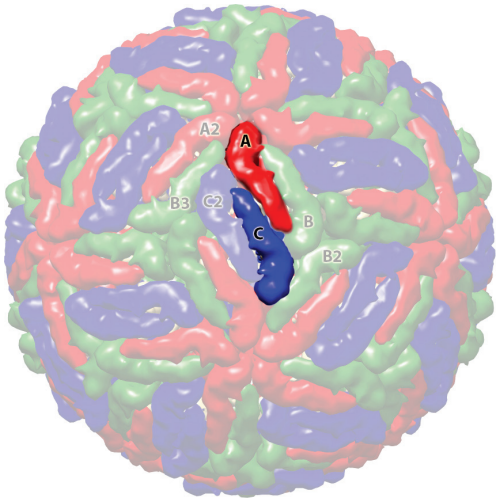
Interface area: 330 Å²

Interfacing residues

Inaccessible residues
Solvent-accessible residues
Residues making Hydrogen/Disulphide bond, Salt bridge or Covalent link
Interfacing residues
**ASA** Accessible Surface Area, Å² **BSA** Buried Surface Area, Å² **ΔG** Solvation energy effect, kcal/mol |||| Buried area percentage, one bar per 10%

| ## | Structure 1 | HSDC | ASA | BSA | ΔG |
|---|---|---|---|---|---|
| 54 | C:ALA 54 | | 74.08 | 7.87 \|\| | 0.13 |
| 76 | C:THR 76 | | 101.27 | 8.42 \| | -0.06 |
| 78 | C:GLY 78 | | 41.94 | 14.11 \|\|\|\| | 0.23 |
| 79 | C:PRO 79 | | 90.36 | 35.23 \|\|\|\| | 0.42 |
| 81 | C:THR 81 | | 90.49 | 14.92 \|\| | 0.20 |
| 86 | C:HIS 86 | | 167.33 | 93.21 \|\|\|\|\|\| | -0.02 |
| 87 | C:GLN 87 | | 80.08 | 4.28 \| | -0.04 |
| 88 | C:GLY 88 | | 43.41 | 13.21 \|\|\|\| | 0.18 |
| 89 | C:GLY 89 | | 15.74 | 4.95 \|\|\|\| | -0.06 |
| 107 | C:LEU 107 | | 104.44 | 11.64 \|\| | 0.19 |
| 135 | C:ASN 135 | | 101.97 | 10.43 \|\| | -0.12 |
| 229 | C:HIS 229 | | 84.52 | 54.11 \|\|\|\|\|\| | 0.13 |
| 230 | C:GLU 230 | | 128.43 | 2.33 \| | -0.03 |
| 232 | C:ALA 232 | | 38.78 | 14.56 \|\|\|\| | 0.23 |
| 234 | C:ASN 234 | | 66.25 | 17.93 \|\|\| | 0.04 |
| 235 | C:TRP 235 | | 25.12 | 3.56 \|\| | -0.04 |
| 236 | C:ASN 236 | | 70.79 | 19.77 \|\|\| | -0.25 |

| ## | Structure 2 | HSDC | ASA | BSA | ΔG |
|---|---|---|---|---|---|
| 54 | A:ALA 54 | | 73.75 | 8.22 \|\| | 0.13 |
| 73 | A:ARG 73 | | 100.87 | 2.48 \| | -0.03 |
| 76 | A:THR 76 | | 99.68 | 7.57 \| | -0.08 |
| 78 | A:GLY 78 | | 42.78 | 19.26 \|\|\|\|\| | 0.31 |
| 79 | A:PRO 79 | | 88.06 | 31.12 \|\|\|\| | 0.32 |
| 81 | A:THR 81 | | 88.55 | 23.46 \|\|\| | 0.26 |
| 86 | A:HIS 86 | | 165.17 | 98.54 \|\|\|\|\|\| | 0.96 |
| 87 | A:GLN 87 | | 82.14 | 6.44 \| | 0.02 |
| 88 | A:GLY 88 | | 44.17 | 15.86 \|\|\|\| | 0.15 |
| 89 | A:GLY 89 | | 14.49 | 3.93 \|\|\| | -0.04 |
| 107 | A:LEU 107 | | 106.14 | 9.63 \| | 0.15 |
| 135 | A:ASN 135 | | 102.88 | 12.00 \|\| | -0.14 |
| 229 | A:HIS 229 | | 88.31 | 52.32 \|\|\|\|\| | 0.13 |
| 232 | A:ALA 232 | | 39.90 | 14.24 \|\|\|\| | 0.23 |
| 234 | A:ASN 234 | | 66.57 | 17.93 \|\|\| | 0.02 |
| 235 | A:TRP 235 | | 24.33 | 2.09 \| | -0.02 |
| 236 | A:ASN 236 | | 71.56 | 7.05 \| | -0.08 |




## E-protein B - C interfaces

Hydrogen bonds

| ## | Structure 1 | Dist. [Å] | Structure 2 |
|---|---|---|---|
| 1 | C:VAL 167[ O ] | 2.72 | B:GLN 391[ N ] |
| 2 | C:SER 169[ O ] | 3.43 | B:GLN 391[ NE2] |
| 3 | C:GLU 170[ OE1] | 3.54 | B:TYR 384[ OH ] |
| 4 | C:GLU 291[ OE1] | 3.10 | B:HIS 347[ NE2] |

Salt bridges

| ## | Structure 1 | Dist. [Å] | Structure 2 |
|---|---|---|---|
| 1 | C:ARG 187[ NE ] | 3.85 | B:ASP 380[ OD2] |
| 2 | C:GLU 291[ OE1] | 3.10 | B:HIS 347[ NE2] |
| 3 | C:GLU 291[ OE2] | 3.93 | B:HIS 347[ NE2] |

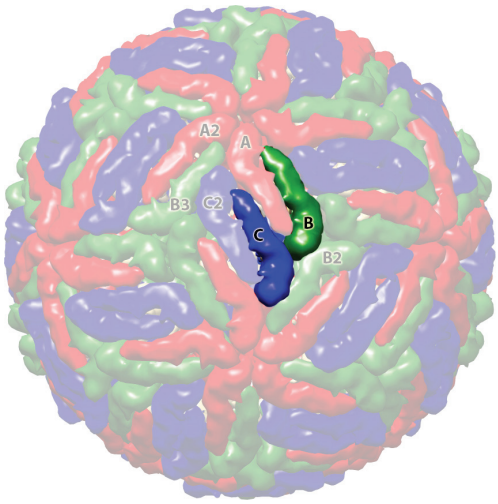
Interface area: 470 Å²

Interfacing residues

Inaccessible residues
Solvent-accessible residues
Residues making Hydrogen/Disulphide bond, Salt bridge or Covalent link
Interfacing residues
**ASA** Accessible Surface Area, Å² **BSA** Buried Surface Area, Å² **ΔG** Solvation energy effect, kcal/mol |||| Buried area percentage, one bar per 10%

| ## | Structure 1 | HSDC | ASA | BSA | ΔG |
|---|---|---|---|---|---|
| 20 | C:ARG 20 | | 128.90 | 8.29 \| | -0.09 |
| 135 | C:ASN 135 | | 101.97 | 40.61 \|\|\|\| | -0.32 |
| 166 | C:THR 166 | | 41.55 | 0.37 \| | -0.00 |
| 167 | C:VAL 167 | H | 77.33 | 62.52 \|\|\|\|\|\|\| | 0.40 |
| 168 | C:SER 168 | | 102.99 | 43.16 \|\|\|\| | 0.51 |
| 169 | C:SER 169 | H | 38.86 | 14.51 \|\|\|\| | -0.11 |
| 170 | C:GLU 170 | H | 140.63 | 79.18 \|\|\|\|\| | 0.25 |
| 185 | C:LEU 185 | | 58.73 | 30.65 \|\|\|\|\| | 0.49 |
| 186 | C:CYS 186 | | 7.64 | 6.26 \|\|\|\|\|\|\| | -0.07 |
| 187 | C:ARG 187 | S | 100.69 | 80.71 \|\|\|\|\|\|\| | -0.59 |
| 188 | C:VAL 188 | | 11.27 | 7.10 \|\|\|\|\| | 0.01 |
| 189 | C:ALA 189 | | 102.23 | 57.29 \|\|\|\|\| | 0.82 |
| 190 | C:SER 190 | | 40.95 | 19.49 \|\|\|\| | 0.31 |
| 291 | C:GLU 291 | HS | 31.26 | 14.15 \|\|\|\| | -0.17 |

| ## | Structure 2 | HSDC | ASA | BSA | ΔG |
|---|---|---|---|---|---|
| 314 | B:TRP 314 | | 71.47 | 5.50 \| | -0.02 |
| 317 | B:ALA 317 | | 65.45 | 17.74 \|\|\| | 0.28 |
| 318 | B:PRO 318 | | 8.80 | 6.62 \|\|\|\|\|\|\| | -0.08 |
| 319 | B:THR 319 | | 68.89 | 2.01 \| | 0.03 |
| 347 | B:HIS 347 | HS | 151.61 | 72.58 \|\|\|\|\| | 0.65 |
| 380 | B:ASP 380 | S | 92.85 | 53.37 \|\|\|\|\| | -0.20 |
| 382 | B:ILE 382 | | 31.09 | 23.34 \|\|\|\|\|\|\| | 0.37 |
| 384 | B:TYR 384 | H | 56.94 | 28.39 \|\|\|\|\| | 0.04 |
| 387 | B:GLU 387 | | 117.56 | 9.08 \| | -0.05 |
| 388 | B:LEU 388 | | 41.44 | 1.84 \| | 0.03 |
| 389 | B:SER 389 | | 55.86 | 48.70 \|\|\|\|\|\|\| | -0.37 |
| 390 | B:HIS 390 | | 62.45 | 54.10 \|\|\|\|\|\|\| | -0.12 |
| 391 | B:GLN 391 | H | 126.80 | 123.60 \|\|\|\|\|\|\|\| | 0.10 |
| 392 | B:TRP 392 | | 36.44 | 6.23 \|\| | 0.07 |
| 393 | B:PHE 393 | | 126.21 | 25.63 \|\|\| | 0.37 |




## E-protein C - B2 interfaces

Salt bridges

| ## | Structure 1 | Dist. [Å] | Structure 2 |
|---|---|---|---|
| 1 | C:ASP 351[ OD2] | 3.18 | B2:ARG 94[ NE ] |
| 2 | C:ASP 351[ OD2] | 3.15 | B2:ARG 94[ NH1] |
| 3 | C:ASP 351[ OD2] | 3.91 | B2:ARG 94[ NH2] |

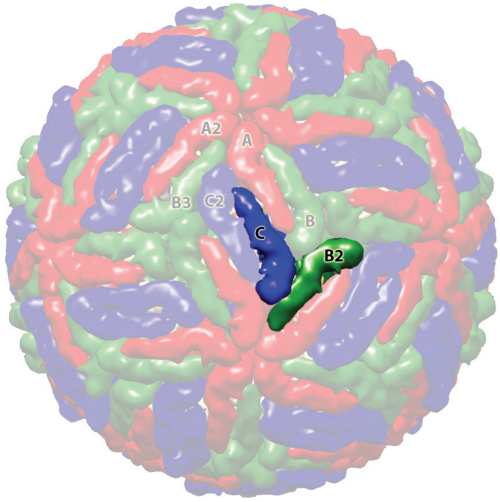
Interface area: 580 Å²

Interfacing residues

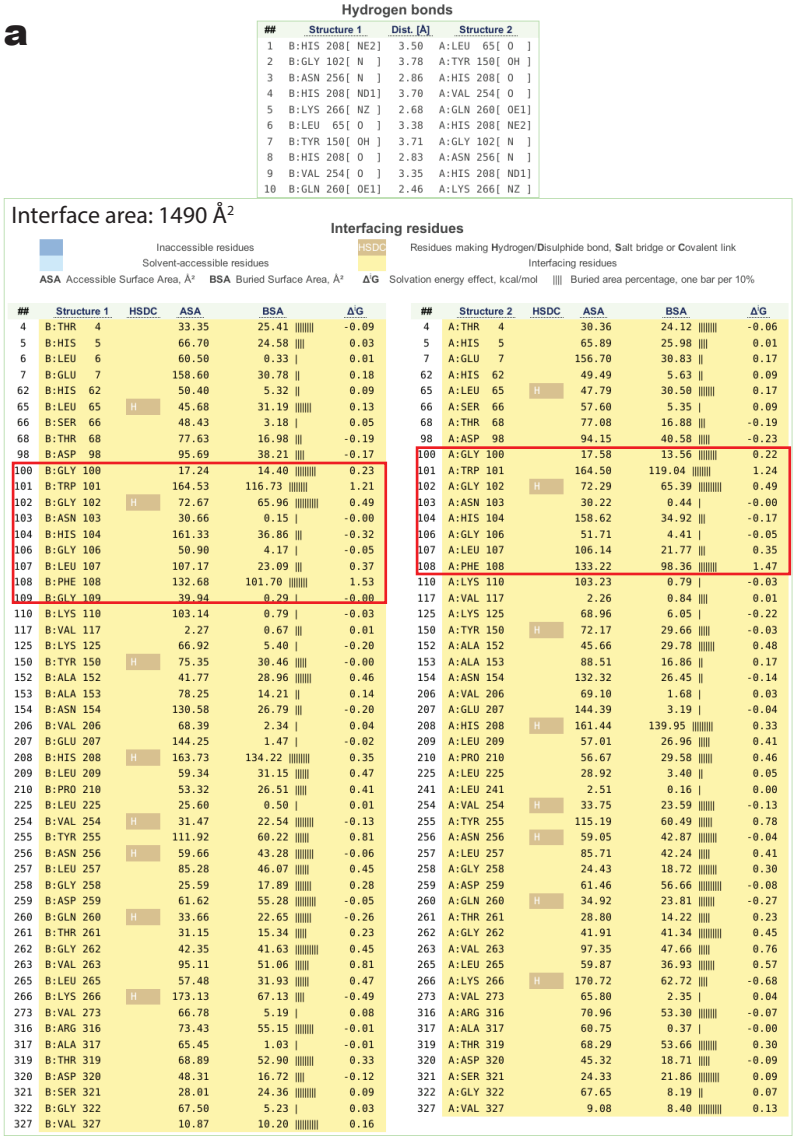
Inaccessible residues
Solvent-accessible residues
Residues making Hydrogen/Disulphide bond, Salt bridge or Covalent link
Interfacing residues
**ASA** Accessible Surface Area, Å² **BSA** Buried Surface Area, Å² **ΔG** Solvation energy effect, kcal/mol |||| Buried area percentage, one bar per 10%

| ## | Structure 1 | HSDC | ASA | BSA | ΔG |
|---|---|---|---|---|---|
| 16 | C:GLN 16 | | 144.34 | 111.23 \|\|\|\|\|\|\| | -0.00 |
| 17 | C:GLY 17 | | 63.69 | 2.51 \| | 0.04 |
| 36 | C:GLU 36 | | 107.96 | 3.44 \| | -0.04 |
| 37 | C:GLY 37 | | 43.21 | 19.99 \|\|\|\|\| | 0.04 |
| 38 | C:LYS 38 | | 37.75 | 10.82 \|\|\| | -0.20 |
| 171 | C:LYS 171 | | 100.58 | 2.37 \| | -0.09 |
| 295 | C:GLU 295 | | 92.73 | 23.57 \|\|\| | 0.08 |
| 296 | C:LYS 296 | | 125.93 | 1.34 \| | 0.02 |
| 297 | C:LEU 297 | | 11.88 | 4.54 \|\|\|\| | -0.05 |
| 298 | C:LYS 298 | | 122.60 | 18.41 \|\| | 0.29 |
| 299 | C:MET 299 | | 42.54 | 2.87 \| | 0.01 |
| 302 | C:LEU 302 | | 103.28 | 78.11 \|\|\|\|\|\|\| | 0.88 |
| 303 | C:THR 303 | | 133.59 | 33.11 \|\|\| | 0.37 |
| 304 | C:TYR 304 | | 60.40 | 0.61 \| | -0.01 |
| 306 | C:MET 306 | | 104.04 | 34.57 \|\|\|\| | 0.68 |
| 309 | C:LYS 309 | | 117.23 | 42.04 \|\|\|\| | -0.39 |
| 339 | C:ARG 339 | | 71.88 | 31.03 \|\|\|\|\| | -0.75 |
| 343 | C:ARG 343 | | 102.64 | 41.94 \|\|\|\|\| | 0.34 |
| 345 | C:VAL 345 | | 8.18 | 1.67 \|\|\| | 0.03 |
| 350 | C:PRO 350 | | 98.86 | 7.97 \| | 0.01 |
| 351 | C:ASP 351 | S | 142.20 | 101.19 \|\|\|\|\|\|\| | -0.57 |
| 353 | C:ASN 353 | | 78.52 | 14.73 \|\| | 0.11 |

| ## | Structure 2 | HSDC | ASA | BSA | ΔG |
|---|---|---|---|---|---|
| 54 | B2:ALA 54 | | 75.40 | 13.90 \|\| | 0.22 |
| 56 | B2:THR 56 | | 29.41 | 0.34 \| | 0.01 |
| 57 | B2:ARG 57 | | 57.79 | 3.16 \| | -0.01 |
| 81 | B2:THR 81 | | 91.51 | 17.91 \|\| | 0.29 |
| 83 | B2:ALA 83 | | 73.87 | 28.37 \|\|\|\| | 0.41 |
| 85 | B2:GLU 85 | | 44.55 | 17.04 \|\|\|\| | -0.16 |
| 86 | B2:HIS 86 | | 167.84 | 111.63 \|\|\|\|\|\| | 0.33 |
| 87 | B2:GLN 87 | | 81.70 | 38.89 \|\|\|\|\| | 0.14 |
| 88 | B2:GLY 88 | | 42.00 | 9.30 \|\|\| | 0.01 |
| 94 | B2:ARG 94 | S | 113.45 | 25.86 \|\|\| | 0.18 |
| 118 | B2:LYS 118 | | 81.47 | 0.26 \| | -0.01 |
| 136 | B2:LYS 136 | | 133.30 | 4.04 \| | -0.06 |
| 227 | B2:TRP 227 | | 54.30 | 11.88 \|\|\| | 0.19 |
| 228 | B2:LYS 228 | | 19.10 | 0.50 \| | 0.01 |
| 229 | B2:HIS 229 | | 87.17 | 79.37 \|\|\|\|\|\|\|\| | 1.10 |
| 230 | B2:GLU 230 | | 126.73 | 27.82 \|\|\| | -0.18 |
| 231 | B2:GLY 231 | | 81.35 | 45.94 \|\|\|\|\| | 0.04 |
| 232 | B2:ALA 232 | | 38.31 | 16.67 \|\|\|\| | 0.25 |
| 233 | B2:ARG 233 | | 218.63 | 105.43 \|\|\|\| | -0.32 |
| 234 | B2:ASN 234 | | 65.04 | 14.67 \|\|\| | -0.17 |
| 236 | B2:ASN 236 | | 71.34 | 0.12 \| | -0.00 |




**Supplementary Figure 2 (continued). Non-quasi equivalent E-protein interfaces in TBEV particle.** The tables show hydrogen bonds, salt bridges and interfacing amino acids with buried surfaces participating in E-protein interactions. The interfaces are shown on the TBEV particles on the right side of the figure.




**Supplementary Figure 3. E-protein dimer interaction interfaces.** (a) Lists of residues forming hydrogen bonds and forming hydrophobic or polar interactions. Residues forming the fusogenic loop (in red frame) from domain II of E-protein are not solvent-accessible. (b) The interfacing residues are shown in green in cartoon representation of the E-protein dimer. E-protein domain I is shown in red, domain II in yellow, domain III in violet, and domain IV in blue. (c) The interfacing residues are shown in green in molecular surface representation of the E-protein dimer.

**a**

Salt bridges

| ## | Structure 1 | Dist. [Å] | Structure 2 |
|---|---|---|---|
| 1 | M1:LYS 38[ NZ ] | 3.88 | E:ASP 222[ OD2] |

Interface area: 740 Å²

E - M1

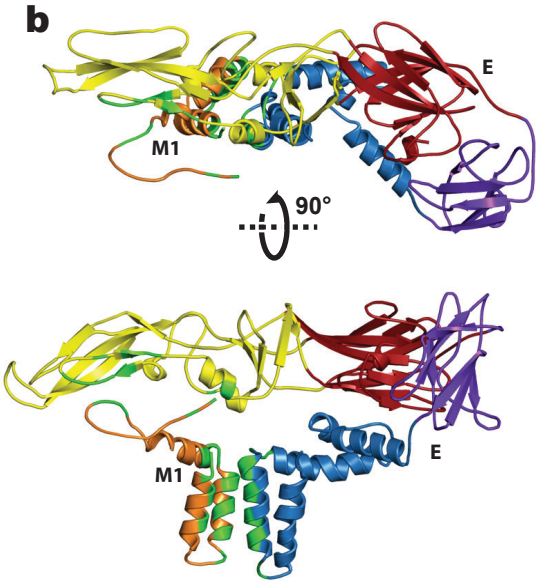
Interfacing residues

Inaccessible residues
Solvent-accessible residues
HSDC Residues making Hydrogen/Disulphide bond, Salt bridge or Covalent link
Interfacing residues
ASA Accessible Surface Area, Å² BSA Buried Surface Area, Å² ΔG Solvation energy effect, kcal/mol |||| Buried area percentage, one bar per 10%

| ## | Structure 1 | HSDC | ASA | BSA | ΔG |
|---|---|---|---|---|---|
| 1 | M1:VAL 2 | | 168.26 | 38.57 \|\|\| | 0.12 |
| 3 | M1:ILE 4 | | 145.17 | 13.05 \| | 0.21 |
| 16 | M1:HIS 17 | | 183.77 | 54.37 \|\|\| | 0.00 |
| 17 | M1:LYS 18 | | 117.71 | 4.17 \| | -0.05 |
| 18 | M1:TRP 19 | | 220.08 | 57.75 \|\|\| | 0.58 |
| 19 | M1:LEU 20 | | 118.18 | 58.76 \|\|\|\|\| | 0.94 |
| 34 | M1:TRP 35 | | 88.91 | 42.50 \|\|\|\|\| | 0.68 |
| 37 | M1:LYS 38 | S | 174.38 | 39.17 \|\|\| | -0.42 |
| 38 | M1:ASN 39 | | 39.32 | 9.15 \|\|\| | -0.14 |
| 40 | M1:LEU 41 | | 157.60 | 38.60 \|\|\| | 0.62 |
| 41 | M1:LEU 42 | | 110.91 | 86.74 \|\|\|\|\|\|\| | 1.39 |
| 44 | M1:ALA 45 | | 43.14 | 0.33 \| | 0.01 |
| 45 | M1:MET 46 | | 52.12 | 20.35 \|\|\|\| | 0.82 |
| 48 | M1:VAL 49 | | 39.84 | 27.85 \|\|\|\|\|\| | 0.45 |
| 51 | M1:LEU 52 | | 145.91 | 7.17 \| | -0.08 |
| 52 | M1:THR 53 | | 86.91 | 47.53 \|\|\|\|\| | 0.76 |
| 53 | M1:LEU 54 | | 167.63 | 45.81 \|\|\| | 0.66 |
| 62 | M1:VAL 63 | | 60.70 | 17.76 \|\|\| | 0.28 |
| 66 | M1:LEU 67 | | 86.54 | 48.10 \|\|\|\|\| | 0.76 |
| 69 | M1:LEU 70 | | 126.94 | 35.68 \|\|\| | 0.44 |
| 70 | M1:ALA 71 | | 29.53 | 12.73 \|\|\|\| | 0.20 |
| 71 | M1:PRO 72 | | 112.27 | 36.66 \|\|\|\| | 0.59 |

| ## | Structure 2 | HSDC | ASA | BSA | ΔG |
|---|---|---|---|---|---|
| 222 | E:ASP 222 | S | 113.57 | 35.97 \|\|\|\| | 0.18 |
| 243 | E:GLU 243 | | 87.32 | 41.83 \|\|\|\|\| | 0.23 |
| 244 | E:PHE 244 | | 26.70 | 0.35 \| | -0.00 |
| 245 | E:GLY 245 | | 20.85 | 4.02 \|\| | 0.06 |
| 246 | E:ALA 246 | | 98.50 | 24.36 \|\|\| | -0.15 |
| 247 | E:PRO 247 | | 23.80 | 0.77 \| | -0.00 |
| 248 | E:HIS 248 | | 120.73 | 16.94 \|\| | 0.27 |
| 253 | E:ASP 253 | | 65.83 | 1.84 \| | -0.03 |
| 255 | E:TYR 255 | | 115.19 | 36.04 \|\|\|\| | 0.48 |
| 256 | E:ASN 256 | | 59.05 | 2.94 \| | -0.03 |
| 257 | E:LEU 257 | | 85.71 | 27.32 \|\|\|\| | 0.44 |
| 266 | E:LYS 266 | | 170.72 | 67.16 \|\|\|\| | -0.45 |
| 447 | E:SER 447 | | 100.39 | 5.20 \| | -0.06 |
| 448 | E:ILE 448 | | 85.36 | 37.20 \|\|\|\|\| | 0.60 |
| 449 | E:PHE 449 | | 70.73 | 33.49 \|\|\|\|\| | 0.38 |
| 451 | E:GLY 451 | | 78.56 | 16.35 \|\|\| | -0.05 |
| 452 | E:VAL 452 | | 63.01 | 49.48 \|\|\|\|\|\| | 0.79 |
| 455 | E:LEU 455 | | 156.06 | 25.15 \|\| | 0.40 |
| 456 | E:PRO 456 | | 46.64 | 36.08 \|\|\|\|\|\| | 0.58 |
| 459 | E:LEU 459 | | 118.40 | 57.33 \|\|\|\|\| | 0.92 |
| 460 | E:LEU 460 | | 77.57 | 42.15 \|\|\|\|\| | 0.67 |
| 463 | E:ALA 463 | | 46.47 | 24.33 \|\|\|\|\| | 0.39 |
| 464 | E:LEU 464 | | 50.05 | 9.44 \|\| | 0.15 |
| 466 | E:TRP 466 | | 167.48 | 16.26 \| | 0.26 |
| 467 | E:LEU 467 | | 85.50 | 60.04 \|\|\|\|\|\| | 0.96 |
| 470 | E:ASN 470 | | 127.69 | 51.14 \|\|\|\|\| | -0.48 |
| 471 | E:MET 471 | | 75.85 | 14.54 \|\| | 0.45 |
| 472 | E:ARG 472 | | 205.71 | 3.19 \| | 0.05 |

**b**




**c**

Hydrogen bonds

| ## | Structure 1 | Dist. [Å] | Structure 2 |
|---|---|---|---|
| 1 | M2:HIS 7[ N ] | 2.96 | E:ALA 267[ O ] |
| 2 | M2:THR 13[ OG1] | 2.81 | E:SER 285[ OG ] |
| 3 | M2:ARG 15[ N ] | 3.87 | E:SER 285[ OG ] |
| 4 | M2:ARG 15[ NH2] | 3.27 | E:GLU 411[ O ] |
| 5 | M2:TRP 19[ N ] | 3.44 | E:VAL 271[ O ] |
| 6 | M2:HIS 17[ O ] | 2.80 | E:VAL 273[ N ] |

Salt bridges

| ## | Structure 1 | Dist. [Å] | Structure 2 |
|---|---|---|---|
| 1 | M2:ARG 15[ NE ] | 3.35 | E:GLU 26[ OE1] |
| 2 | M2:ARG 15[ NE ] | 3.10 | E:GLU 26[ OE2] |
| 3 | M2:ARG 15[ NH2] | 3.58 | E:GLU 26[ OE2] |

Interface area: 1500 Å²

E - M2

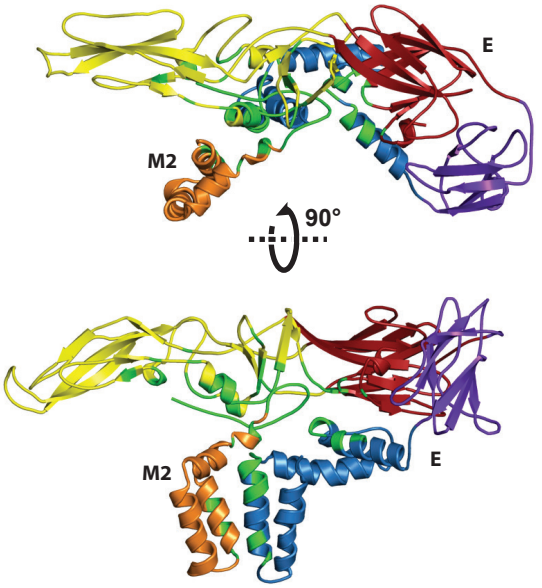
Interfacing residues

Inaccessible residues
Solvent-accessible residues
HSDC Residues making Hydrogen/Disulphide bond, Salt bridge or Covalent link
Interfacing residues
ASA Accessible Surface Area, Å² BSA Buried Surface Area, Å² ΔG Solvation energy effect, kcal/mol |||| Buried area percentage, one bar per 10%

| ## | Structure 1 | HSDC | ASA | BSA | ΔG |
|---|---|---|---|---|---|
| 1 | M2:VAL 2 | | 206.91 | 118.80 \|\|\|\|\| | 1.42 |
| 2 | M2:LEU 3 | | 156.56 | 26.53 \|\| | -0.23 |
| 3 | M2:ILE 4 | | 151.90 | 139.01 \|\|\|\|\|\|\| | 2.03 |
| 4 | M2:PRO 5 | | 96.80 | 43.29 \|\|\|\|\| | 0.43 |
| 5 | M2:SER 6 | | 68.59 | 33.81 \|\|\|\| | 0.41 |
| 6 | M2:HIS 7 | H | 152.70 | 149.06 \|\|\|\|\|\|\|\| | 1.11 |
| 7 | M2:ALA 8 | | 65.97 | 28.85 \|\|\|\| | 0.07 |
| 8 | M2:GLN 9 | | 147.68 | 64.57 \|\|\|\|\| | 0.15 |
| 9 | M2:GLY 10 | | 34.91 | 8.56 \|\|\| | 0.11 |
| 10 | M2:GLU 11 | | 135.80 | 70.63 \|\|\|\|\| | -0.52 |
| 11 | M2:LEU 12 | | 157.10 | 125.24 \|\|\|\|\|\| | 1.33 |
| 12 | M2:THR 13 | H | 124.51 | 91.15 \|\|\|\|\|\| | 0.62 |
| 13 | M2:GLY 14 | | 46.06 | 25.62 \|\|\|\|\| | 0.06 |
| 14 | M2:ARG 15 | HS | 252.67 | 189.73 \|\|\|\|\|\| | -1.41 |
| 15 | M2:GLY 16 | | 58.65 | 31.14 \|\|\|\|\| | 0.35 |
| 16 | M2:HIS 17 | H | 188.51 | 57.90 \|\|\| | 0.05 |
| 17 | M2:LYS 18 | | 126.40 | 52.14 \|\|\|\| | 0.74 |
| 18 | M2:TRP 19 | H | 227.71 | 161.90 \|\|\|\|\|\| | 1.60 |
| 19 | M2:LEU 20 | | 116.07 | 24.93 \|\|\| | 0.22 |
| 20 | M2:GLU 21 | | 105.55 | 9.05 \| | 0.14 |
| 23 | M2:SER 24 | | 49.20 | 25.91 \|\|\|\|\| | 0.40 |
| 24 | M2:LEU 25 | | 124.88 | 57.02 \|\|\|\|\| | 0.89 |
| 27 | M2:HIS 28 | | 115.23 | 40.51 \|\|\|\| | 0.37 |
| 28 | M2:LEU 29 | | 84.45 | 5.02 \| | 0.08 |
| 57 | M2:VAL 58 | | 137.52 | 22.60 \|\| | 0.36 |
| 58 | M2:THR 59 | | 72.76 | 27.30 \|\|\|\| | 0.44 |
| 61 | M2:ALA 62 | | 57.38 | 2.01 \| | 0.03 |
| 65 | M2:VAL 66 | | 77.63 | 10.56 \|\| | 0.17 |

| ## | Structure 2 | HSDC | ASA | BSA | ΔG |
|---|---|---|---|---|---|
| 8 | E:ASN 8 | | 41.58 | 26.65 \|\|\|\|\| | -0.10 |
| 26 | E:GLU 26 | S | 38.98 | 24.74 \|\|\|\|\| | -0.14 |
| 27 | E:LEU 27 | | 29.91 | 15.95 \|\|\|\| | -0.18 |
| 28 | E:GLY 28 | | 51.76 | 15.67 \|\|\| | 0.09 |
| 61 | E:LEU 61 | | 1.85 | 0.17 \| | 0.00 |
| 196 | E:GLN 196 | | 62.96 | 5.16 \| | -0.06 |
| 197 | E:THR 197 | | 9.07 | 4.39 \|\|\|\| | -0.03 |
| 208 | E:HIS 208 | | 161.44 | 0.49 \| | -0.01 |
| 209 | E:LEU 209 | | 57.01 | 10.55 \|\| | 0.17 |
| 210 | E:PRO 210 | | 56.67 | 16.90 \|\|\| | 0.27 |
| 213 | E:TRP 213 | | 13.63 | 12.85 \|\|\|\|\|\|\| | -0.08 |
| 214 | E:GLN 214 | | 23.49 | 19.33 \|\|\|\|\|\| | -0.15 |
| 215 | E:VAL 215 | | 6.58 | 6.07 \|\|\|\|\|\| | 0.10 |
| 216 | E:HIS 216 | | 96.46 | 50.31 \|\|\|\|\| | 0.55 |
| 219 | E:TRP 219 | | 82.01 | 63.26 \|\|\|\|\|\| | 0.48 |
| 222 | E:ASP 222 | | 113.57 | 10.18 \| | -0.12 |
| 223 | E:LEU 223 | | 35.78 | 21.25 \|\|\|\| | 0.34 |
| 224 | E:ALA 224 | | 68.55 | 42.78 \|\|\|\|\| | 0.36 |
| 225 | E:LEU 225 | | 28.92 | 25.52 \|\|\|\|\|\| | 0.41 |
| 240 | E:ARG 240 | | 93.83 | 19.25 \|\|\| | -0.03 |
| 241 | E:LEU 241 | | 2.51 | 2.36 \|\|\|\|\|\|\| | 0.04 |
| 243 | E:GLU 243 | | 87.32 | 6.08 \| | -0.05 |
| 257 | E:LEU 257 | | 85.71 | 16.15 \|\| | 0.26 |
| 260 | E:GLN 260 | | 34.92 | 11.11 \|\|\| | -0.05 |
| 263 | E:VAL 263 | | 97.35 | 29.79 \|\|\| | 0.48 |
| 264 | E:LEU 264 | | 11.50 | 10.83 \|\|\|\|\|\| | 0.16 |
| 265 | E:LEU 265 | | 59.87 | 22.95 \|\|\| | 0.07 |
| 266 | E:LYS 266 | | 170.72 | 8.35 \| | 0.05 |
| 267 | E:ALA 267 | H | 53.05 | 50.41 \|\|\|\|\|\| | 0.33 |
| 268 | E:LEU 268 | | 15.83 | 15.83 \|\|\|\|\|\|\| | -0.05 |
| 269 | E:ALA 269 | | 94.66 | 76.99 \|\|\|\|\|\| | 0.54 |
| 270 | E:GLY 270 | | 84.73 | 66.40 \|\|\|\|\|\| | 0.16 |
| 271 | E:VAL 271 | H | 39.43 | 36.75 \|\|\|\|\|\|\| | 0.19 |
| 272 | E:PRO 272 | | 57.98 | 55.13 \|\|\|\|\|\|\| | 0.87 |
| 273 | E:VAL 273 | H | 65.80 | 48.10 \|\|\|\|\|\| | 0.69 |
| 284 | E:LYS 284 | | 117.94 | 35.97 \|\|\|\| | 0.08 |
| 285 | E:SER 285 | H | 37.95 | 37.58 \|\|\|\|\|\|\| | -0.07 |
| 286 | E:GLY 286 | | 8.08 | 3.18 \|\|\| | 0.05 |
| 287 | E:HIS 287 | | 21.90 | 6.95 \|\|\| | -0.63 |
| 408 | E:LYS 408 | | 43.60 | 6.78 \|\| | 0.11 |
| 411 | E:GLU 411 | H | 113.13 | 20.20 \|\| | -0.00 |
| 412 | E:ARG 412 | | 47.56 | 9.79 \|\|\| | 0.15 |
| 414 | E:THR 414 | | 60.46 | 19.08 \|\|\| | 0.05 |
| 415 | E:VAL 415 | | 104.97 | 39.72 \|\|\|\| | 0.64 |
| 416 | E:ILE 416 | | 36.94 | 32.64 \|\|\|\|\|\| | 0.50 |
| 450 | E:GLY 450 | | 49.85 | 2.59 \| | 0.04 |
| 451 | E:GLY 451 | | 78.56 | 49.15 \|\|\|\|\| | -0.13 |
| 452 | E:VAL 452 | | 63.01 | 2.24 \| | 0.04 |
| 453 | E:GLY 453 | | 39.67 | 35.15 \|\|\|\|\|\| | 0.44 |
| 454 | E:PHE 454 | | 113.79 | 54.85 \|\|\|\|\| | 0.70 |
| 455 | E:LEU 455 | | 156.06 | 76.93 \|\|\|\|\| | 1.23 |
| 457 | E:LYS 457 | | 32.18 | 8.19 \|\|\| | 0.13 |
| 458 | E:LEU 458 | | 93.99 | 9.20 \| | 0.15 |
| 459 | E:LEU 459 | | 118.40 | 10.39 \| | 0.17 |
| 466 | E:TRP 466 | | 167.48 | 36.10 \|\|\| | 0.11 |
| 469 | E:LEU 469 | | 128.24 | 13.55 \|\| | 0.22 |

**d**




**Supplementary Figure 4. E-M interaction interfaces.** Interfacing amino acid residues were identified by PDBePISA. Every E-protein interacts with two M-proteins in the heterotetramer. (a, c) The tables show hydrogen bonds, salt bridges, and interfacing amino acids with the buried surface. (b, d) Cartoon representation of E/M-protein interfaces shown in tables. The interfacing residues are shown in green, M-protein in orange, and E-protein domain I in red, domain II in yellow, domain III in violet, and domain IV in blue.

**Flavivirus envelope protein alignement**

```
Q01299    175| TMGEYGDVSLLCRVASGVDLAQTVILELDKTVEHLPTAWQVHRDWFNDLALPWKHEGA-- | 232 | TBEVH
P14336    175| TMGEYGDVSLLCRVASGVDLAQTVILELDKTVEHLPTAWQVHRDWFNDLALPWKHEGA-- | 232 | TBEVW
P07720    175| TMGDYGDVSLLCRVASGVDLAQTVILELDKTSEHLPTAWQVHRDWFNDLALPWKHEGA-- | 232 | TBEVS
P29837    175| TLGDYGDVSLLCRVASGVDLAQTVVLALDKTHEHLPTAWQVHRDWFNDLALPWKHDGA-- | 232 | LANVT
Q04538    175| RLGDYGDVSLTCKVASGIDVAQTVVMSLDSSKDHLPSAWQVHRDWFEDLALPWKHKDN-- | 232 | POWV
P06935    175| KLGEYGEVTVDCEPRSGIDTSAYYVMSVGE------KSFLVHREWFMDLNLPWSSAGS-- | 226 | WNV
P27395    179| KLGDYGEVTLDCEPRSGLNTEAFYVMTVGS------KSFLVHREWFHDLALPWTSPSS-- | 230 | JEV
P17763    174| QLTDYGALTLDCSPRTGLDFNEMVLLTMEK------KSWLVHKQWFLDLPLPWTSGASTS | 227 | DENV1
P29990    174| ELTGYGTVTMECSPRTGLDFNEMVLLQMEN------KAWLVHRQWFLDLPLPWLPGADTQ | 227 | DENV2
Q6YMS4    172| ILPEYGTLGLECSPRTGLDFNEMILLTMKN------KAWMVHRQWFFDLPLPWASGATTE | 225 | DENV3
Q2YHF0    174| KLPDYGELTLDCEPRSGIDFNEMILMKMKT------KTWLVHKQWFLDLPLPWTAGADTL | 227 | DENV4
P03314    171| EFIGYGKATLECQVQTAVDFGNSYIAEMET------ESWIVDRQWAQDLTLPWQSGSG-- | 222 | YFV
KJ776791  179| TLGGFGSLGLDCEPRTGLDFSDLYYLTMNN------KHWLVHKEWFHDIPLPWHAGADTG | 232 | ZIKV
```

tick-borne flaviviruses

mosquito-borne flaviviruses

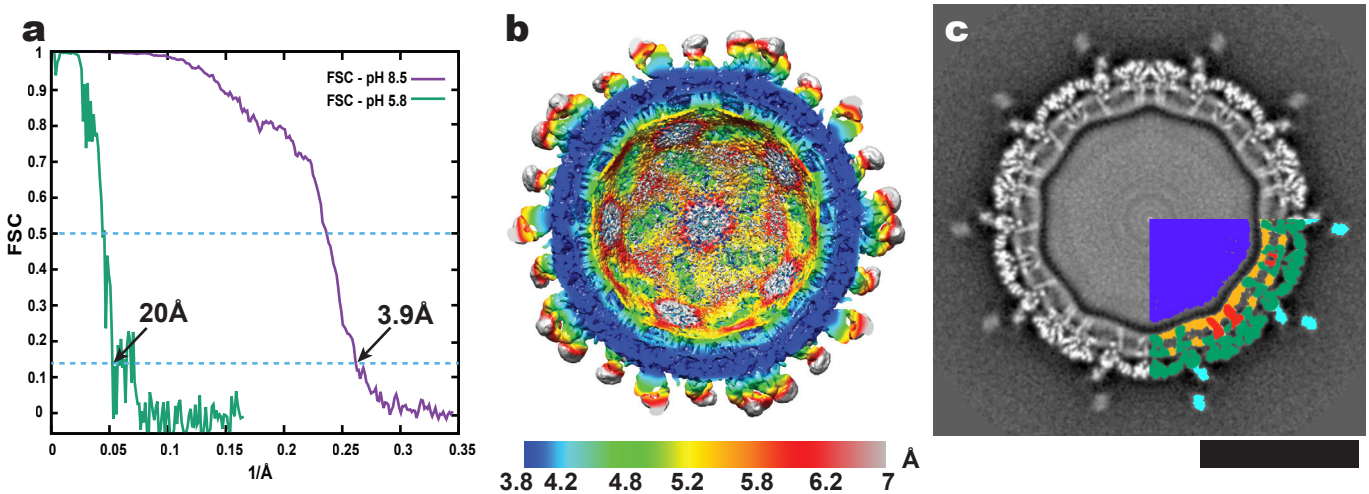
```
Q01299    233| -RNWNNAERLVEFGAPHAVKMDVYNLGDQTGVLLKALAGVPVAHIEGTK---YHLKSGHV | 288 | TBEVH
P14336    233| -QNWNNAERLVEFGAPHAVKMDVYNLGDQTGVLLKALAGVPVAHIEGTK---YHLKSGHV | 288 | TBEVW
P07720    233| -QNWNNAERLVEFGAPHAVKMDVYNLGDQTGVLLKSLAGVPVAHIDGTK---YHLKSGHV | 288 | TBEVS
P29837    233| -EAWNEAGRLVEFGTPHAVKMDVFNLGDQTGVLLKSLAGVPVASIEGTK---YHLKSGHV | 288 | LANVT
Q04538    233| -QDWNSVEKLVEFGPPHAVKMDVFNLGDQTAVLLKSLAGVPLASVEGQK---YHLKSGHV | 288 | POWV
P06935    227| -TTWRNRETLMEFEEPHATKQSVVALGSQEGALHQALAGAIPVEFSSNT---VKLTSGHL | 282 | WNV
P27395    231| -TAWRNRELLMEFEGAHATKQSVVALGSQEGGLHQALAGAIVVEYSS-S---VKLTSGHL | 285 | JEV
P17763    228| QETWNRQDLLVTFKTAHAKKQEVVVLGSQEGAMHTALTGATEIQTSGT----TTIFAGHL | 283 | DENV1
P29990    228| GSNWIQKETLVTFKNPHAKKQDVVVLGSQEGAMHTALTGATEIQMSSG----NLLFTGHL | 283 | DENV2
Q6YMS4    226| TPTWNRKELLVTFKNAHAKKQEVVVLGSQEGAMHTALTGATEIQNSGG----TSIFAGHL | 281 | DENV3
Q2YHF0    228| EVHWNHKERMVTFKVPHAKRQDVTVLGSQEGAMHSALAGATEVDSGDG----NHMFAGHL | 283 | DENV4
P03314    223| -GVWREMHHLVEFEPPHAATIRVLALGNQEGSLKTALTGAMRVTKDTNDNNLYKLHGGHV | 281 | YFV
KJ776791  233| TPHWNNKEALVEFKDAHAKRQTVVVLGSQEGAVHTALAGALEAEMDGAK---GRLSSGHL | 289 | ZIKV
```

```
Q01299    401| RVFQKTKKGIERLTVIGEHAWDFGSAGGFLSSIGKALHTVLGGAFNSIFGGVGFLPKLLL | 460 | TBEVH
P14336    401| RVFQKTKKGIERLTVIGEHAWDFGSAGGFLSSIGKAVHTVLGGAFNSIFGGVGFLPKLLL | 460 | TBEVW
P07720    401| RVFQKTRKGIERLTVIGEHAWDFGSTGGFLTSVGKALHTVLGGAFNSLFGGVGFLPKILV | 460 | TBEVS
P29837    401| RVLQKTRKGIERLTVLGEHAWDFGSVGGVMTSIGRAMHTVLGGAFNTLLGGVGFLPKILL | 460 | LANVT
Q04538    402| RMFEKTRRGLERLSVVGEHAWDFGSVGGVLSSVGKAIHTVLGGAFNTLFGGVGFIPKMLL | 461 | POWV
P06935    402| KAFTTTLRGAQRLAALGDTAWDFGSVGGVFTSVGKAIHQVFGGAFRSLFGGMSWITQGLL | 461 | WNV
P27395    405| KAFSTTLKGAQRLAALGDTAWDFGSIGGVFNSIGRAVHQVFGGAFRTLFGGMSWITQGLM | 464 | JEV
P17763    400| KMFEATARGARRMAILGDTAWDFGSIGGVFTSVGKLIHQIFGTAYGVLFSGVSWTMKIGI | 459 | DENV1
P29990    400| QMFETTMRGAKRMAILGDTAWDFGSLGGVFTSIGKALHQVFGAIYGAAFSGVSWTMKILI | 459 | DENV2
Q6YMS4    398| KMFEATERGARRMAILGDTAWDFGSVGGVLNSLGKMVHQIFGSAYTALFSGVSWVMKIGI | 457 | DENV3
Q2YHF0    400| KMFESTYRGAKRMAILGETAWDFGSVGGLLTSLGKAVHQVFGSVYTTMFGGVSWMVRILI | 459 | DENV4
P03314    398| KLFTQTMKGVERLAVMGDTAWDFSSAGGFFTSVGKGIHTVFGSAFQGLFGGLNWITKVIM | 457 | YFV
KJ776791  409| KAFEATVRGAKRMAVLGDTAWDFGSVGGALNSLGKGIHQIFGAAFKSLFGGMSWFSQILI | 468 | ZIKV
```

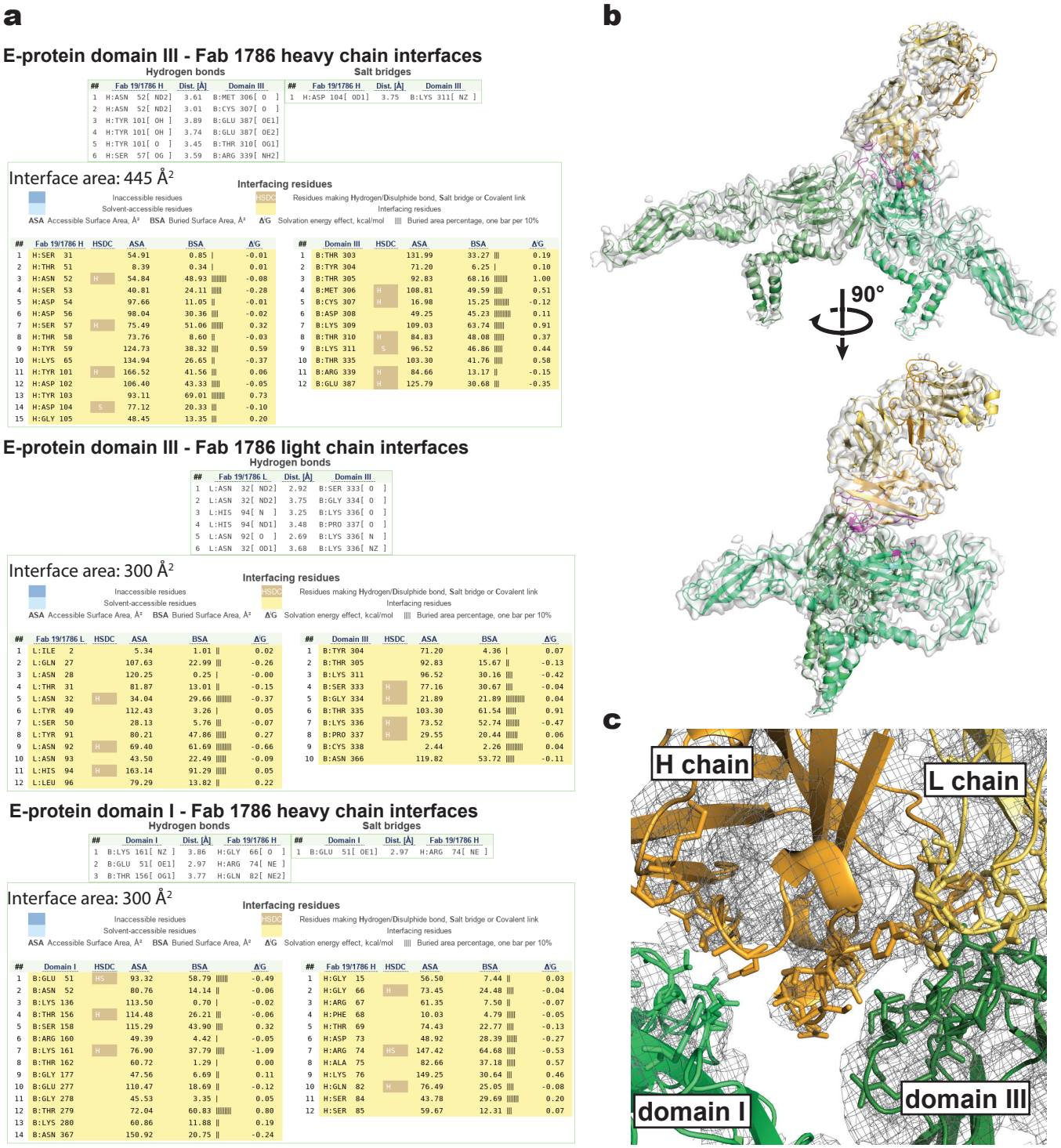
**Flavivirus membrane protein alignement**

```
Q01299    1 | SVLIPSHAQGELTGRGHKWLEGDSLRTHLTRVEGWVWKNRLLALAMVTVVWLTLESVVTR | 60 | TBEVH
P14336    1 | SVLIPSHAQGELTGRGHKWLEGDSLRTHLTRVEGWVWKNKLLALAMVTVVWLTLESVVTR | 60 | TBEVW
P07720    1 | SVLIPSHAQGDLTGRGHKWLEGDSLRTHLTRVEGWVWKNKVLTLAVIAVVWLTVESVVTR | 60 | TBEVS
P29837    1 | SVLIPSHAQRDLTGRGHQWLEGEAVKAHLTRVEGWVWKNKLFTLSLVMVAWLMVDGLLPR | 60 | LANVT
Q04538    1 | SVVIPTHAQKDMVGRGHAWLKGDNIRDHVTRVEGWMWKNKLLTAAIVALAWLMVDSWMAR | 60 | POWV
P06935    1 | SLTVQTHGESTLANKKGAWLDSTKATRYLVKTESWILRNPGYALVAAVIGWMLGSNTMQR | 60 | WNV
P27395    1 | SVSVQTHGESSLVNKKEAWLDSTKATRYLMKTENWIIRNPGYAFLAAVLGWMLGSNNGQR | 60 | JEV
P17763    1 | SVALAPHVGLGLETRTETWMSSEGAWKQIQKVETWALRHPGFTVIALFLAHAIGTSITQK | 60 | DENV1
P29990    1 | SVALVPHVGMGLETRTETWMSSEGAWKHVQRIETWILRHPGFTMMAAILAYTIGTTHFQR | 60 | DENV2
Q6YMS4    1 | SVALAPHVGMGLDTRTQTWMSAEGAWRQVEKVETWALRHPGFTILALFLAHYIGTSLTQK | 60 | DENV3
Q2YHF0    1 | SVALTPHSGMGLETRAETWMSSEGAWKHAQRVESWILRNPGFALLAGFMAYMIGQTGIQR | 60 | DENV4
P03314    1 | AIDLPTHENHGLKTRQEKWMTGRMGERQLQKIERWFVRNPFFAVTALTIAYLVGSNMTQR | 60 | YFV
KJ776791  1 | AVTLPSHSTRKLQTRSQTWLESREYTKHLIRVENWIFRNPGFALAAAAIAWLLGSSTSQK | 60 | ZIKV
```

**Supplementary Figure 5. Multiple sequence alignment of flavivirus envelope and membrane proteins.** Sequences were aligned using Clustal Omega. Parts of the alignments are shown in the figure. Histidines that may be involved in the putative pH-dependent conformational switch are highlighted in red. Uniprot IDs are provided on the left side of the sequences (except for ZIKV, where Genbank ID is shown). The position of the amino acids in the aligned sequence and the virus names are shown on the right. TBEVH – Tick-borne encephalitis virus strain Hypr; TBEVW - Tick-borne encephalitis virus European subtype (strain Neudoerfl); TBEVS - Tick-borne encephalitis virus Far Eastern subtype (strain Sofjin); LANVT - Langat virus (strain TP21); POWV - Tick-borne powassan virus (strain LB); WNV - West Nile virus (strain 956); JEV - Japanese encephalitis virus (strain SA-14); DENV1 - Dengue virus type 1 (strain Nauru/West Pac/1974); DENV2 - Dengue virus type 2 (strain Thailand-/16681/1984); DENV3 - Dengue virus type 3 (strain Sri Lanka/1266/2000); DENV4 - Dengue virus type 4 (strain Thailand-/0348/1991); YFV - Yellow fever virus (strain 17D vaccine); ZIKV - Zika virus (strain H/PF/2013). Conservation of a residue is denoted by: "*" - absolute conservation; ":" - conservation of amino acids with strongly similar properties; "." – conservation of amino acids with weakly similar properties.




**Supplementary Figure 6. Cryo-EM reconstruction of TBEV Fab 19/1786 complex.** (a) Fourier shell correlation (FSC) curves of final reconstructions of TBEV-Fab 19/1786 complex at pH 8.5 (purple) and at pH 5.8 (green) calculated according to "gold standard". (b) Local resolution of cryo-EM map of TBEV-Fab 19/1786 complex. The display shows a cut-away half map colored according to the local resolution. Parts of the map with resolution worse than 7 Å are shown in grey. The non-sharpened electron density map was used for the display. (c) Central slice of electron-density map perpendicular to virus fivefold axis. The overall shape and features of the TBEV particle remained intact after attachment of Fab 19/1786 fragment. The lower right quadrant of the slice is color-coded as follows: nucleocapsid – blue; inner and outer membrane leaflets – orange; M-proteins – red; E-proteins – green; Fab 19/1786 attached to virus surface – cyan.




**Supplementary Figure 7. E-protein – Fab 19/1786 interaction interfaces next to threefold axis.** Interfacing amino acids were identified using PDBePISA. (a) Tables show hydrogen bonds, salt bridges, and amino acids with buried surface. (b) Cartoon representation of E-protein – Fab 19/1786 interfaces shown in tables. E-proteins are shown in green, Fab 19/1786 heavy chain in orange, Fab 19/1786 light chain in yellow, and residues forming the interface in magenta. (c) Detail of interaction interface.

**a**

### E-protein domain III - Fab 1786 heavy chain interfaces

Hydrogen bonds

| ## | Fab 19/1786 H | Dist. [Å] | Domain III |
|---|---|---|---|
| 1 | H:SER 53[ OG ] | 3.58 | C:LYS 309[ NZ ] |
| 2 | H:ASP 56[ OD2] | 2.82 | C:LYS 309[ NZ ] |
| 3 | H:SER 53[ O ] | 2.90 | C:LYS 309[ NZ ] |
| 4 | H:TYR 101[ O ] | 3.87 | C:THR 310[ OG1] |
| 5 | H:SER 57[ OG ] | 3.84 | C:ARG 339[ NH2] |

Salt bridges

| ## | Fab 19/1786 H | Dist. [Å] | Domain III |
|---|---|---|---|
| 1 | H:ASP 56[ OD2] | 2.82 | C:LYS 309[ NZ ] |
| 2 | H:ASP 104[ OD1] | 3.90 | C:LYS 311[ NZ ] |

Interface area: 440 Å²

Interfacing residues

Inaccessible residues
Solvent-accessible residues
HSDC Residues making Hydrogen/Disulphide bond, Salt bridge or Covalent link
Interfacing residues
ASA Accessible Surface Area, Å² BSA Buried Surface Area, Å² ΔG Solvation energy effect, kcal/mol |||| Buried area percentage, one bar per 10%

| ## | Fab 19/1786 H | HSDC | ASA | BSA | ΔG |
|---|---|---|---|---|---|
| 1 | H:SER 30 | | 57.11 | 5.75 \| | -0.07 |
| 2 | H:SER 31 | | 52.54 | 9.86 \| | 0.12 |
| 3 | H:ASN 52 | | 53.02 | 45.59 \|\|\|\|\|\|\| | 0.04 |
| 4 | H:SER 53 | H | 48.62 | 34.92 \|\|\|\|\|\|\| | -0.34 |
| 5 | H:ASP 54 | | 66.83 | 3.82 \| | 0.06 |
| 6 | H:ASP 56 | HS | 117.62 | 22.50 \|\| | -0.10 |
| 7 | H:SER 57 | H | 73.05 | 51.64 \|\|\|\|\|\|\| | 0.27 |
| 8 | H:THR 58 | | 77.33 | 11.91 \|\| | -0.14 |
| 9 | H:TYR 59 | | 108.26 | 26.33 \|\|\| | 0.42 |
| 10 | H:LYS 65 | | 125.17 | 12.99 \|\| | -0.41 |
| 11 | H:TYR 101 | H | 167.57 | 35.60 \|\|\| | 0.10 |
| 12 | H:ASP 102 | | 101.93 | 43.78 \|\|\|\|\| | -0.01 |
| 13 | H:TYR 103 | | 102.14 | 78.44 \|\|\|\|\|\|\| | 0.84 |
| 14 | H:ASP 104 | S | 85.25 | 25.17 \|\|\| | -0.14 |
| 15 | H:GLY 105 | | 49.72 | 15.63 \|\|\|\| | 0.24 |

| ## | Domain III | HSDC | ASA | BSA | ΔG |
|---|---|---|---|---|---|
| 1 | C:THR 303 | | 128.43 | 12.34 \| | 0.17 |
| 2 | C:TYR 304 | | 75.44 | 2.02 \| | -0.00 |
| 3 | C:THR 305 | | 87.47 | 58.32 \|\|\|\|\|\| | 0.93 |
| 4 | C:MET 306 | | 95.61 | 48.76 \|\|\|\|\| | 0.44 |
| 5 | C:CYS 307 | | 16.54 | 16.18 \|\|\|\|\|\|\|\| | -0.11 |
| 6 | C:ASP 308 | | 50.24 | 44.08 \|\|\|\|\|\|\| | 0.14 |
| 7 | C:LYS 309 | HS | 107.40 | 76.31 \|\|\|\|\|\|\| | -1.23 |
| 8 | C:THR 310 | H | 85.27 | 45.35 \|\|\|\|\| | 0.40 |
| 9 | C:LYS 311 | S | 100.62 | 44.28 \|\|\|\|\| | 0.31 |
| 10 | C:PHE 332 | | 8.09 | 0.31 \| | 0.00 |
| 11 | C:GLY 334 | | 28.90 | 9.08 \|\|\|\| | 0.15 |
| 12 | C:THR 335 | | 105.67 | 49.87 \|\|\|\|\| | 0.55 |
| 13 | C:ARG 339 | H | 79.45 | 10.42 \|\| | -0.12 |
| 14 | C:GLU 387 | | 129.87 | 34.18 \|\|\| | -0.44 |

### E-protein domain III - Fab 1786 light chain interfaces

Hydrogen bonds

| ## | Fab 19/1786 L | Dist. [Å] | Domain III |
|---|---|---|---|
| 1 | L:ASN 32[ ND2] | 2.81 | C:SER 333[ O ] |
| 2 | L:ASN 32[ ND2] | 3.56 | C:GLY 334[ O ] |
| 3 | L:HIS 94[ N ] | 3.53 | C:LYS 336[ O ] |
| 4 | L:HIS 94[ ND1] | 3.09 | C:LYS 336[ O ] |
| 5 | L:HIS 94[ ND1] | 3.76 | C:PRO 337[ O ] |
| 6 | L:TYR 91[ O ] | 3.85 | C:LYS 336[ N ] |
| 7 | L:ASN 32[ OD1] | 3.54 | C:LYS 336[ NZ ] |
| 8 | L:ASN 92[ O ] | 3.68 | C:ASN 366[ ND2] |

Interface area: 275 Å²

Interfacing residues

Inaccessible residues
Solvent-accessible residues
HSDC Residues making Hydrogen/Disulphide bond, Salt bridge or Covalent link
Interfacing residues
ASA Accessible Surface Area, Å² BSA Buried Surface Area, Å² ΔG Solvation energy effect, kcal/mol |||| Buried area percentage, one bar per 10%

| ## | Fab 19/1786 L | HSDC | ASA | BSA | ΔG |
|---|---|---|---|---|---|
| 1 | L:ILE 2 | | 5.45 | 0.65 \|\| | 0.01 |
| 2 | L:GLN 27 | | 103.52 | 10.03 \| | -0.11 |
| 3 | L:THR 31 | | 87.81 | 5.16 \| | -0.06 |
| 4 | L:ASN 32 | H | 41.31 | 35.50 \|\|\|\|\|\|\| | -0.44 |
| 5 | L:SER 50 | | 33.75 | 0.86 \| | -0.01 |
| 6 | L:TYR 91 | H | 75.48 | 44.15 \|\|\|\|\| | 0.24 |
| 7 | L:ASN 92 | H | 78.83 | 64.26 \|\|\|\|\|\|\| | -0.57 |
| 8 | L:ASN 93 | | 52.04 | 24.09 \|\|\|\| | -0.08 |
| 9 | L:HIS 94 | H | 157.42 | 91.55 \|\|\|\|\| | 0.11 |
| 10 | L:LEU 96 | | 89.25 | 14.87 \|\| | 0.24 |

| ## | Domain III | HSDC | ASA | BSA | ΔG |
|---|---|---|---|---|---|
| 1 | C:THR 305 | | 87.47 | 24.87 \|\|\| | 0.28 |
| 2 | C:LYS 311 | | 100.62 | 1.66 \| | -0.01 |
| 3 | C:SER 333 | H | 73.07 | 24.86 \|\|\| | -0.12 |
| 4 | C:GLY 334 | H | 28.90 | 19.82 \|\|\|\|\| | 0.06 |
| 5 | C:THR 335 | | 105.67 | 55.80 \|\|\|\|\| | 0.83 |
| 6 | C:LYS 336 | H | 88.19 | 64.80 \|\|\|\|\|\| | -0.20 |
| 7 | C:PRO 337 | H | 38.77 | 28.00 \|\|\|\|\| | 0.24 |
| 8 | C:CYS 338 | | 0.16 | 0.16 \|\|\|\|\|\|\|\| | 0.00 |
| 9 | C:ASN 366 | H | 115.96 | 40.10 \|\|\|\| | -0.22 |

### E-protein domain II - Fab 1786 heavy chain interfaces

Hydrogen bonds

| ## | Domain II | Dist. [Å] | Fab 19/1786 H |
|---|---|---|---|
| 1 | B:LYS 69[ NZ ] | 2.09 | H:GLY 55[ O ] |
| 2 | B:LYS 69[ NZ ] | 3.04 | H:ASP 54[ O ] |
| 3 | B:GLU 84[ N ] | 3.30 | H:ASP 56[ OD1] |
| 4 | B:VAL 70[ O ] | 3.40 | H:ARG 74[ NH2] |

Interface area: 365 Å²

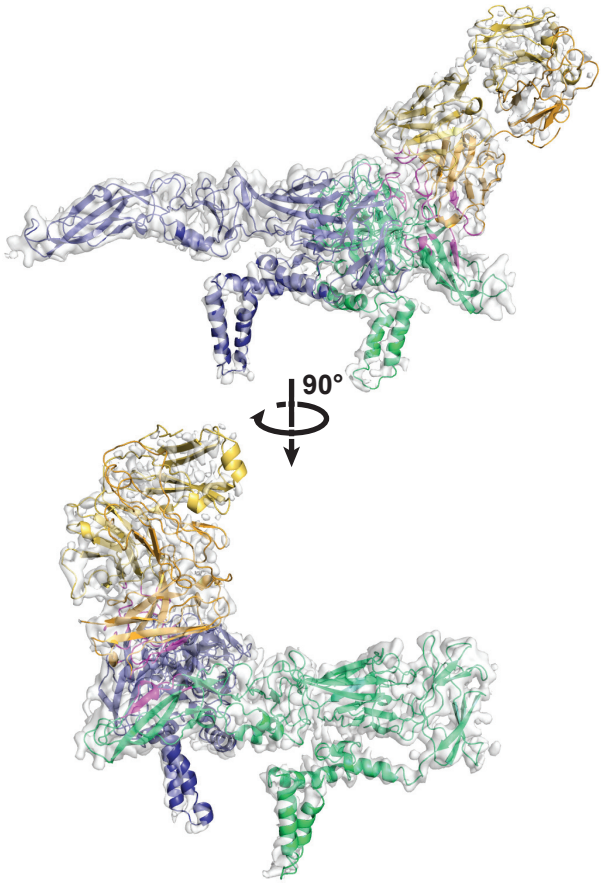
Interfacing residues

Inaccessible residues
Solvent-accessible residues
HSDC Residues making Hydrogen/Disulphide bond, Salt bridge or Covalent link
Interfacing residues
ASA Accessible Surface Area, Å² BSA Buried Surface Area, Å² ΔG Solvation energy effect, kcal/mol |||| Buried area percentage, one bar per 10%

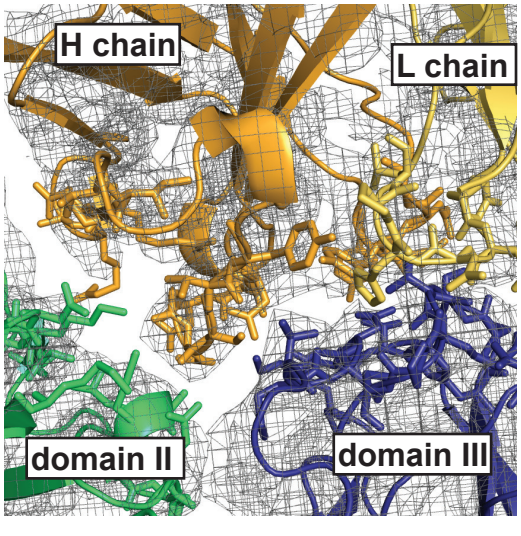
| ## | Domain II | HSDC | ASA | BSA | ΔG |
|---|---|---|---|---|---|
| 1 | B:LYS 64 | | 97.54 | 1.97 \| | -0.07 |
| 2 | B:SER 66 | | 44.45 | 10.21 \|\|\| | 0.16 |
| 3 | B:ASP 67 | | 80.90 | 64.57 \|\|\|\|\|\|\| | -0.64 |
| 4 | B:LYS 69 | H | 102.89 | 77.40 \|\|\|\|\|\|\| | -0.71 |
| 5 | B:VAL 70 | H | 43.91 | 9.44 \|\|\| | -0.08 |
| 6 | B:ALA 71 | | 15.69 | 14.23 \|\|\|\|\|\|\|\| | 0.23 |
| 7 | B:ALA 72 | | 25.67 | 4.02 \|\| | -0.05 |
| 8 | B:ARG 73 | | 102.46 | 6.97 \| | -0.15 |
| 9 | B:ALA 80 | | 8.03 | 0.67 \| | 0.01 |
| 10 | B:THR 81 | | 125.01 | 1.35 \| | -0.02 |
| 11 | B:LEU 82 | | 29.64 | 21.59 \|\|\|\|\|\|\| | 0.35 |
| 12 | B:ALA 83 | | 79.73 | 41.44 \|\|\|\|\| | 0.55 |
| 13 | B:GLU 84 | H | 29.92 | 28.13 \|\|\|\|\|\|\|\| | -0.09 |
| 14 | B:GLN 87 | | 96.17 | 39.08 \|\|\|\| | -0.40 |
| 15 | B:LYS 118 | | 68.84 | 22.04 \|\|\| | 0.32 |
| 16 | B:LYS 251 | | 126.74 | 15.88 \|\| | -0.07 |

| ## | Fab 19/1786 H | HSDC | ASA | BSA | ΔG |
|---|---|---|---|---|---|
| 1 | H:SER 53 | | 48.62 | 0.12 \| | -0.00 |
| 2 | H:ASP 54 | H | 66.83 | 41.46 \|\|\|\|\|\| | -0.38 |
| 3 | H:GLY 55 | H | 35.40 | 27.59 \|\|\|\|\|\| | -0.28 |
| 4 | H:ASP 56 | H | 117.62 | 103.65 \|\|\|\|\|\|\| | -0.47 |
| 5 | H:SER 57 | | 73.05 | 16.53 \|\|\| | 0.25 |
| 6 | H:THR 58 | | 77.33 | 20.00 \|\|\| | 0.30 |
| 7 | H:GLY 66 | | 65.11 | 1.84 \| | -0.02 |
| 8 | H:THR 69 | | 80.04 | 14.57 \|\| | 0.23 |
| 9 | H:ILE 70 | | 10.93 | 7.37 \|\|\|\|\|\| | -0.08 |
| 10 | H:SER 71 | | 57.12 | 21.43 \|\|\|\| | 0.34 |
| 11 | H:ARG 72 | | 35.51 | 24.51 \|\|\|\|\|\| | -0.06 |
| 12 | H:ASP 73 | | 38.34 | 0.37 \| | -0.00 |
| 13 | H:ARG 74 | H | 158.46 | 74.33 \|\|\|\|\| | -1.19 |
| 14 | H:ALA 75 | | 87.91 | 8.02 \| | 0.13 |
| 15 | H:LYS 76 | | 141.42 | 7.69 \| | 0.12 |

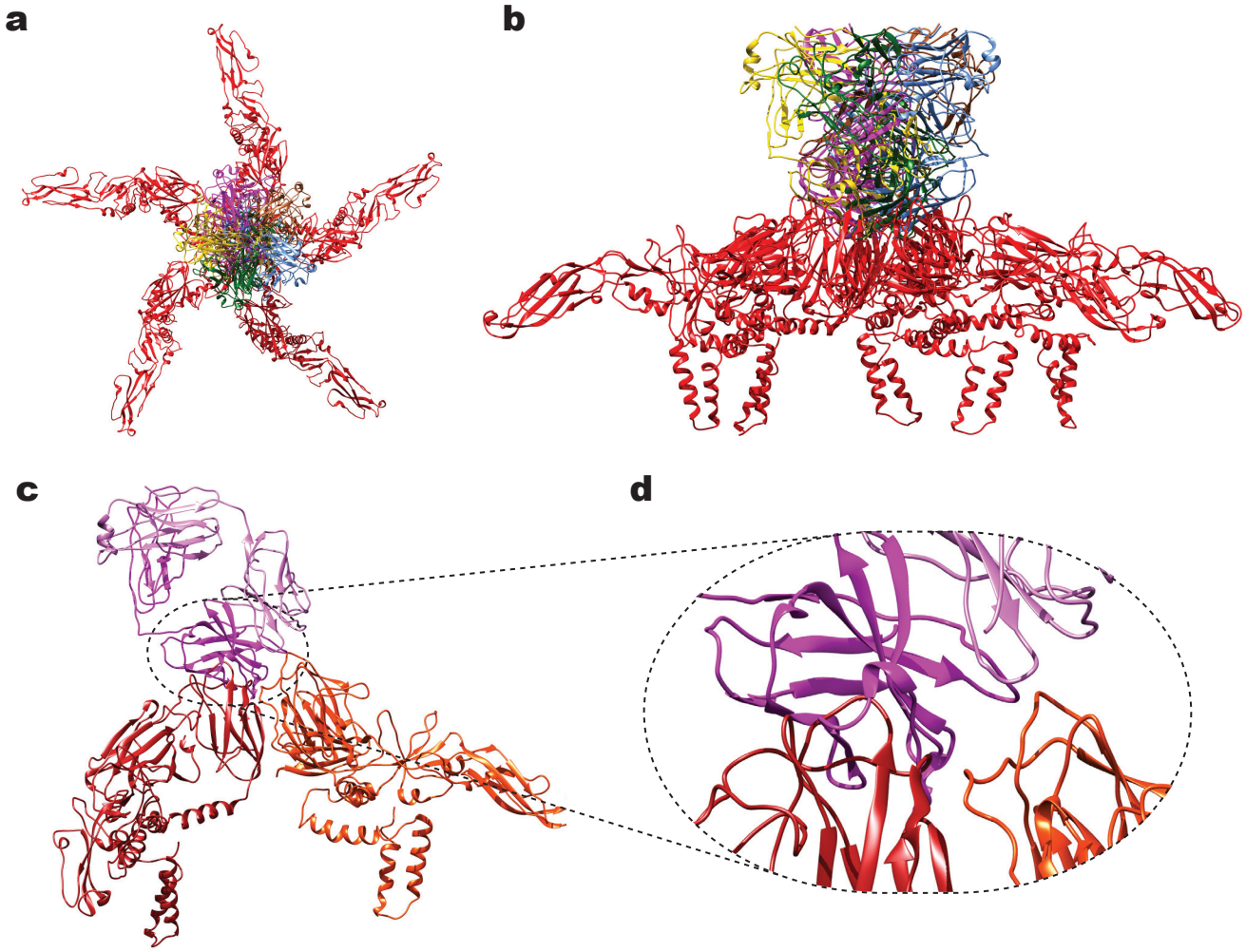
**b**



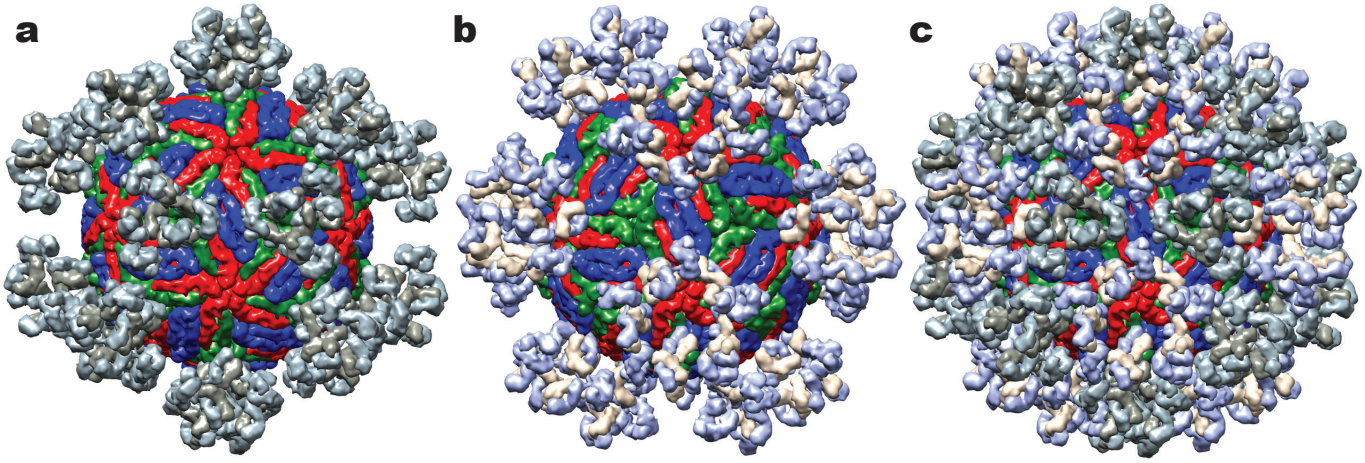

**c**




**Supplementary Figure 8. E-protein – Fab 19/1786 interaction interfaces close to fivefold axis.** Interfacing amino acid residues were identified using PDBePISA. (a) Tables show hydrogen bonds, salt bridges, and amino acids with buried surface. (b) Cartoon representation of E-protein – Fab 19/1786 interfaces show in tables. E-proteins are shown in green and blue, Fab 19/1786 heavy chain in orange, Fab 19/1786 light chain in yellow, and residues forming the interface in magenta. (c) Detail of interaction interface.




**Supplementary Figure 9. Steric hindrance prevents attachment of Fab 19/1786 fragments to unoccupied E-proteins.** Molecular model shows clashes of Fab fragments with each other caused by simulated attachment of Fab 19/1786 to unoccupied E-proteins close to fivefold axis (a, b). The Fab 19/1786 could not bind to the third E-protein within the icosahedral asymmetric unit because upon binding to domain III of the unoccupied E-protein, the heavy chain of the Fab would clash with domain III of a neighboring E-protein (c) and (d). E-proteins are shown in red; Fab 19/1786 fragments in multiple colors.




**Supplementary Figure 10. TBEV particle fully occupied by mouse IgG1 antibodies.** Model of TBEV virion covered with IgG1 antibodies on sites corresponding to epitopes of Fab 19/1786. PDB:1IGY was superposed onto Fab 19/1786 attached to virion surface next to virus threefold axis (a), close to virus fivefold axis (b), and on both interaction sites (c). The attachment produces clash-free coverage of the particle with IgG1.