Energetic Profile-Based Protein Comparison: A New and Fast Approach for Structural and Evolutionary analysis

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|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Based** | **Method** | **Time** | **ARI** | | | | **Class Error** | | | |
| **3** | **4** | **5** | **6** | **3** | **4** | **5** | **6** |
| Sequence | **CPE** | **0.9 sec** | 0.50 | **0.95** | 0.94 | 0.92 | 0.22 | **0.08** | 0.1 | 0.11 |
| **TM Vec** | 89 sec | 0.16 | 0.48 | 0.87 | **0.86** | 0.34 | 0.22 | 0.12 | **0.14** |
| **MSA (ClustalW)** | 72 sec | 0.49 | 0.49 | 0.32 | 0.32 | 0.22 | 0.22 | 0.29 | 0.29 |
| Structure | **SPE** | **3 min** | **1** | **0.95** | 0.93 | 0.66 | **0** | **0.08** | 0.11 | 0.26 |
| **RMSD** | 70 min | 0.50 | 0.50 | 0.36 | **0.73** | 0.22 | 0.22 | 0.22 | **0.17** |
| **TM score** | 9.7 h | 0.50 | **0.56** | 0.40 | 0.40 | 0.22 | **0.17** | 0.24 | 0.24 |

Table S1. The results of clustering using the Adjusted Rand Index (ARI) and class error

Table S2. The PDB IDs of spike proteins.

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **pdbID** | **length** | **virus** | **pdbID** | **length** | **virus** | **pdbID** | **length** | **virus** | **pdbID** | **length** | **virus** |
| **6XM5A** | **1057** | **SARS-CoV-2** | **6CRZA** | **1068** | **SARS-CoV** | **6Q04B** | **1159** | **MERS-CoV** | **6ZGFC** | **1060** | **SARS-CoV-2** |
| **6ZP2A** | **1097** | **SARS-CoV-2** | **6CRWA** | **1068** | **SARS-CoV** | **6ACKB** | **1065** | **SARS-CoV** | **6ZGEC** | **1098** | **SARS-CoV-2** |
| **6ZP1A** | **1017** | **SARS-CoV-2** | **5W9JA** | **463** | **MERS-CoV** | **6ACJB** | **1065** | **SARS-CoV** | **6Z97C** | **991** | **SARS-CoV-2** |
| **6ZP0A** | **1030** | **SARS-CoV-2** | **5XLRA** | **1022** | **SARS-CoV** | **6ACGB** | **1065** | **SARS-CoV** | **7BYRC** | **973** | **SARS-CoV-2** |
| **6ZOZA** | **1069** | **SARS-CoV-2** | **5X5FA** | **1141** | **MERS-CoV** | **6ACDB** | **1065** | **SARS-CoV** | **6X6PC** | **1017** | **SARS-CoV-2** |
| **6ZOYA** | **1021** | **SARS-CoV-2** | **5X58A** | **1054** | **SARS-CoV** | **6ACCB** | **1065** | **SARS-CoV** | **6Z43C** | **991** | **SARS-CoV-2** |
| **6ZOXA** | **1017** | **SARS-CoV-2** | **5WRGA** | **736** | **SARS-CoV** | **5W9OD** | **463** | **MERS-CoV** | **6X2CC** | **971** | **SARS-CoV-2** |
| **6XEYA** | **1034** | **SARS-CoV-2** | **6ZP7B** | **930** | **SARS-CoV-2** | **5W9ND** | **463** | **MERS-CoV** | **6X2AC** | **961** | **SARS-CoV-2** |
| **6ZGIA** | **1098** | **SARS-CoV-2** | **6ZP5B** | **943** | **SARS-CoV-2** | **5W9MD** | **457** | **MERS-CoV** | **6X29C** | **972** | **SARS-CoV-2** |
| **6ZGGA** | **1069** | **SARS-CoV-2** | **6ZOWB** | **930** | **SARS-CoV-2** | **5W9LB** | **726** | **MERS-CoV** | **6WPTC** | **952** | **SARS-CoV-2** |
| **6ZGFA** | **1060** | **SARS-CoV-2** | **6ZHDB** | **992** | **SARS-CoV-2** | **5W9KD** | **462** | **MERS-CoV** | **6WPSE** | **955** | **SARS-CoV-2** |
| **6ZGEA** | **1098** | **SARS-CoV-2** | **6XM5B** | **1056** | **SARS-CoV-2** | **5W9JD** | **463** | **MERS-CoV** | **6VYBC** | **960** | **SARS-CoV-2** |
| **6Z97A** | **995** | **SARS-CoV-2** | **6ZP2B** | **1097** | **SARS-CoV-2** | **5W9HD** | **463** | **MERS-CoV** | **6VXXC** | **972** | **SARS-CoV-2** |
| **6XCMA** | **966** | **SARS-CoV-2** | **6ZP1B** | **1017** | **SARS-CoV-2** | **5XLRB** | **1022** | **SARS-CoV** | **6VSBC** | **973** | **SARS-CoV-2** |
| **6X6PA** | **1017** | **SARS-CoV-2** | **6ZP0B** | **1030** | **SARS-CoV-2** | **5X5FB** | **1141** | **MERS-CoV** | **6Q07C** | **1159** | **MERS-CoV** |
| **6X2CA** | **971** | **SARS-CoV-2** | **6ZOZB** | **1069** | **SARS-CoV-2** | **5X5CB** | **1141** | **MERS-CoV** | **6Q06C** | **1159** | **MERS-CoV** |
| **6X2BA** | **963** | **SARS-CoV-2** | **6ZOYB** | **1021** | **SARS-CoV-2** | **5X5BB** | **1053** | **SARS-CoV** | **6Q05C** | **1159** | **MERS-CoV** |
| **6X2AA** | **966** | **SARS-CoV-2** | **6ZOXB** | **1017** | **SARS-CoV-2** | **5X58B** | **1053** | **SARS-CoV** | **6Q04C** | **1159** | **MERS-CoV** |
| **6X29A** | **972** | **SARS-CoV-2** | **6XEYB** | **1034** | **SARS-CoV-2** | **5WRGB** | **736** | **SARS-CoV** | **6NB3C** | **1169** | **MERS-CoV** |
| **6WPTA** | **945** | **SARS-CoV-2** | **6XKLB** | **976** | **SARS-CoV-2** | **6ZP7C** | **943** | **SARS-CoV-2** | **6ACCC** | **1065** | **SARS-CoV** |
| **6WPSA** | **955** | **SARS-CoV-2** | **7C2LB** | **1055** | **SARS-CoV-2** | **6ZP5C** | **930** | **SARS-CoV-2** | **6CS1C** | **1068** | **SARS-CoV** |
| **6VYBA** | **966** | **SARS-CoV-2** | **6ZGIB** | **1098** | **SARS-CoV-2** | **6ZOWC** | **943** | **SARS-CoV-2** | **6CS0C** | **1069** | **SARS-CoV** |
| **6VXXA** | **972** | **SARS-CoV-2** | **6ZGHB** | **1077** | **SARS-CoV-2** | **6ZHDC** | **990** | **SARS-CoV-2** | **6CRZC** | **1069** | **SARS-CoV** |
| **6Q07A** | **1159** | **MERS-CoV** | **6ZGFB** | **1060** | **SARS-CoV-2** | **6XM5C** | **1036** | **SARS-CoV-2** | **6CRXC** | **1069** | **SARS-CoV** |
| **6Q06A** | **1159** | **MERS-CoV** | **6ZGEB** | **1098** | **SARS-CoV-2** | **6ZP2C** | **1097** | **SARS-CoV-2** | **6CRWC** | **1068** | **SARS-CoV** |
| **6Q05A** | **1159** | **MERS-CoV** | **7BYRB** | **998** | **SARS-CoV-2** | **6ZP1C** | **1017** | **SARS-CoV-2** | **5W9OG** | **463** | **MERS-CoV** |
| **6Q04A** | **1159** | **MERS-CoV** | **6X6PB** | **1017** | **SARS-CoV-2** | **6ZP0C** | **1030** | **SARS-CoV-2** | **5W9NG** | **457** | **MERS-CoV** |
| **6NB6A** | **1052** | **SARS-CoV** | **6Z43B** | **992** | **SARS-CoV-2** | **6ZOZC** | **1070** | **SARS-CoV-2** | **5W9ME** | **726** | **MERS-CoV** |
| **6NB4A** | **1169** | **MERS-CoV** | **6X2CB** | **971** | **SARS-CoV-2** | **6ZOYC** | **1021** | **SARS-CoV-2** | **5W9LC** | **726** | **MERS-CoV** |
| **6NB3A** | **1169** | **MERS-CoV** | **6X29B** | **972** | **SARS-CoV-2** | **6ZOXC** | **1017** | **SARS-CoV-2** | **5W9JG** | **463** | **MERS-CoV** |
| **6ACKA** | **1065** | **SARS-CoV** | **6WPSB** | **955** | **SARS-CoV-2** | **6XEYC** | **1030** | **SARS-CoV-2** | **5W9HG** | **463** | **MERS-CoV** |
| **6ACJA** | **1065** | **SARS-CoV** | **6VXXB** | **972** | **SARS-CoV-2** | **6XKLC** | **976** | **SARS-CoV-2** | **5XLRC** | **1022** | **SARS-CoV** |
| **6ACGA** | **1065** | **SARS-CoV** | **6VSBB** | **973** | **SARS-CoV-2** | **7C2LC** | **1049** | **SARS-CoV-2** | **5X5BC** | **1053** | **SARS-CoV** |
| **6ACDA** | **1065** | **SARS-CoV** | **6Q07B** | **1159** | **MERS-CoV** | **6ZGIC** | **1098** | **SARS-CoV-2** | **5X58C** | **1052** | **SARS-CoV** |
| **6ACCA** | **1065** | **SARS-CoV** | **6Q06B** | **1159** | **MERS-CoV** | **6ZGHC** | **1080** | **SARS-CoV-2** | **5WRGC** | **736** | **SARS-CoV** |
| **6CS0A** | **1068** | **SARS-CoV** | **6Q05B** | **1159** | **MERS-CoV** | **6ZGGC** | **1067** | **SARS-CoV-2** |  |  |  |

Table S3. The results of 1-NN classification on SARS Proteome using CPE.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| SARS\_Proteome | ac | pr | re | f1 |
| E\_protein | 99.68 | 100 | 96.55 | 98 |
| N\_C-terminaldomain | 99.68 | 100 | 100 | 100 |
| N\_N-terminaldomain | 99.68 | 99.82 | 100 | 100 |
| NSP1\_protein | 99.68 | 100 | 95.83 | 98 |
| NSP10\_protein | 99.68 | 100 | 100 | 100 |
| NSP12\_protein | 99.68 | 100 | 100 | 100 |
| NSP13\_protein | 99.68 | 100 | 100 | 100 |
| NSP14\_protein | 99.68 | 100 | 100 | 100 |
| NSP15\_protein | 99.68 | 100 | 100 | 100 |
| NSP16\_protein | 99.68 | 99.61 | 100 | 100 |
| NSP2\_protein | 99.68 | 100 | 100 | 100 |
| NSP3\_cd21525\_SUD\_C\_SARS-CoV\_Nsp3 | 99.68 | 99.2 | 100 | 100 |
| NSP3\_cd21557\_Macro\_X\_Nsp3-like | 99.68 | 99.19 | 99.19 | 99 |
| NSP3\_cd21717\_TM\_Y\_SARS-CoV-like\_Nsp3\_C | 99.68 | 100 | 99.19 | 100 |
| NSP3\_cd21732\_betaCoV\_PLPro | 99.68 | 99.18 | 100 | 100 |
| NSP3\_cd21822\_SARS-CoV-like\_Nsp3\_NAB | 99.68 | 98.33 | 99.16 | 99 |
| NSP3\_cl00019\_Macro\_SF | 99.68 | 100 | 97.62 | 99 |
| NSP3\_cl13138\_SUD-M | 99.68 | 99.17 | 95.97 | 98 |
| NSP3\_cl13772\_DUF3655 | 99.68 | 100 | 100 | 100 |
| NSP5\_protein | 99.68 | 100 | 99.59 | 100 |
| NSP7\_protein | 99.68 | 100 | 100 | 100 |
| NSP8\_protein | 99.68 | 99.5 | 100 | 100 |
| NSP9\_protein | 99.68 | 98.21 | 99.4 | 99 |
| orf3a\_protein | 99.68 | 100 | 100 | 100 |
| orf7a\_protein | 99.68 | 100 | 100 | 100 |
| orf8\_protein | 99.68 | 100 | 100 | 100 |
| orf9b\_protein | 99.68 | 91.3 | 100 | 95 |
| S\_protein | 99.68 | 100 | 100 | 100 |
| 29 | 99.68 | 99.4110714 | 99.375 | 99.4642857 |

Table S4. The results of 1-NN classification on SARS Proteome using SPE.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Proteom | ac | pr | re | f1 |
| E\_protein | 99.73 | 100 | 96.55 | 98 |
| N\_C-terminaldomain | 99.73 | 100 | 99.82 | 100 |
| N\_N-terminaldomain | 99.73 | 100 | 100 | 100 |
| NSP1\_protein | 99.73 | 100 | 95.83 | 98 |
| NSP10\_protein | 99.73 | 99.55 | 100 | 100 |
| NSP12\_protein | 99.73 | 100 | 100 | 100 |
| NSP13\_protein | 99.73 | 100 | 100 | 100 |
| NSP14\_protein | 99.73 | 100 | 100 | 100 |
| NSP15\_protein | 99.73 | 100 | 100 | 100 |
| NSP16\_protein | 99.73 | 100 | 100 | 100 |
| NSP2\_protein | 99.73 | 100 | 100 | 100 |
| NSP3\_cd21525\_SUD\_C\_SARS-CoV\_Nsp3 | 99.73 | 96.88 | 100 | 98 |
| NSP3\_cd21557\_Macro\_X\_Nsp3-like | 99.73 | 100 | 100 | 100 |
| NSP3\_cd21717\_TM\_Y\_SARS-CoV-like\_Nsp3\_C | 99.73 | 100 | 100 | 100 |
| NSP3\_cd21732\_betaCoV\_PLPro | 99.73 | 100 | 100 | 100 |
| NSP3\_cd21822\_SARS-CoV-like\_Nsp3\_NAB | 99.73 | 98.35 | 100 | 99 |
| NSP3\_cl00019\_Macro\_SF | 99.73 | 97.22 | 83.33 | 90 |
| NSP3\_cl13138\_SUD-M | 99.73 | 100 | 99.19 | 100 |
| NSP3\_cl13772\_DUF3655 | 99.73 | 100 | 100 | 100 |
| NSP5\_protein | 99.73 | 100 | 100 | 100 |
| NSP7\_protein | 99.73 | 100 | 100 | 100 |
| NSP8\_protein | 99.73 | 100 | 100 | 100 |
| NSP9\_protein | 99.73 | 98.81 | 100 | 99 |
| orf3a\_protein | 99.73 | 100 | 100 | 100 |
| orf7a\_protein | 99.73 | 96.3 | 100 | 98 |
| orf8\_protein | 99.73 | 95 | 100 | 97 |
| orf9b\_protein | 99.73 | 100 | 100 | 100 |
| S\_protein | 99.73 | 100 | 100 | 100 |

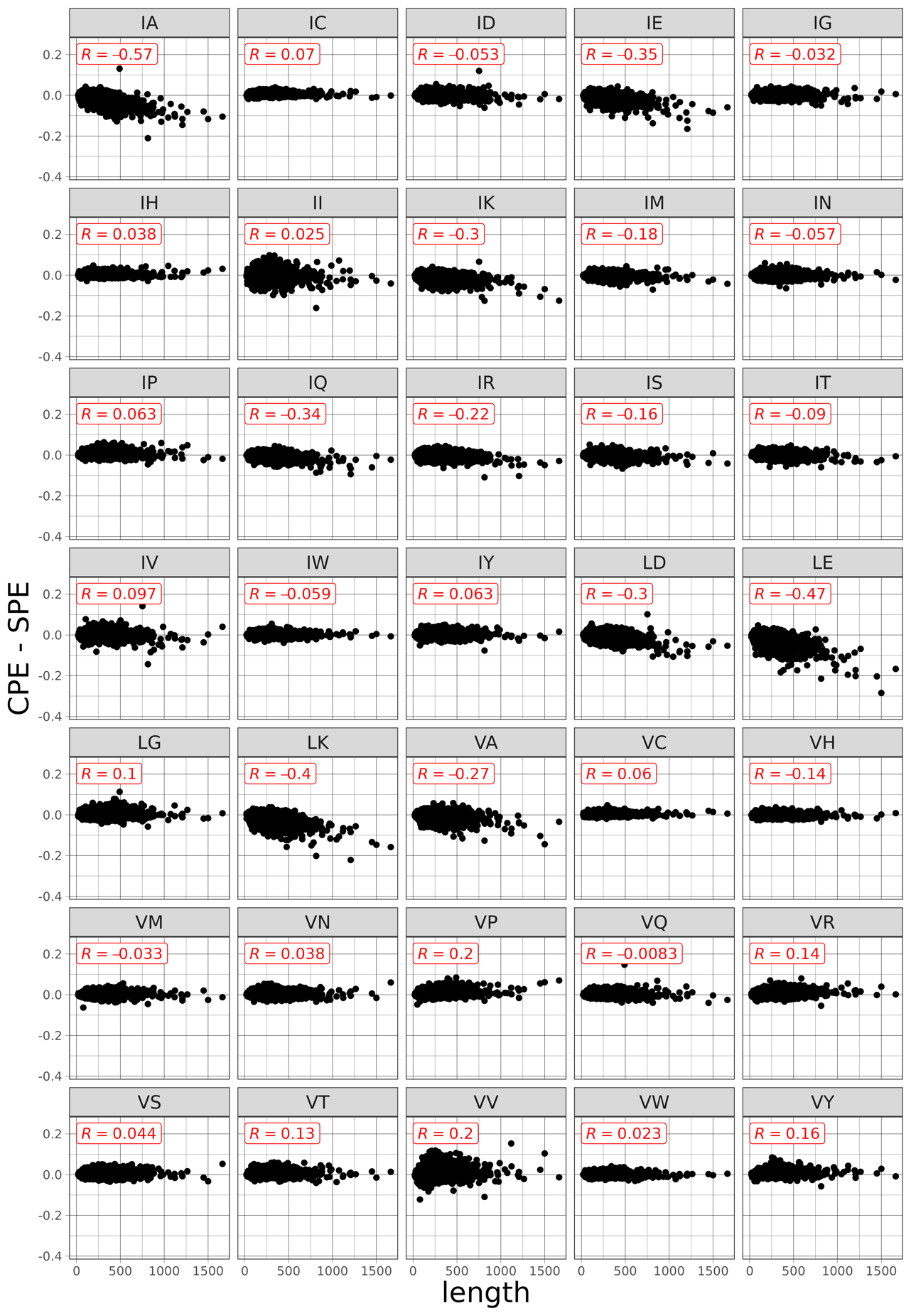
Table S5. The results of 1-NN classification on SARS Proteome using TM-Vec.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | ac | pr | re | f1 |
| Average | 99.66 | 99.4157143 | 99.1167857 | 99.25 |
| E\_protein | 99.66 | 98.31 | 100 | 99 |
| N\_C-terminaldomain | 99.66 | 100 | 99.82 | 100 |
| N\_N-terminaldomain | 99.66 | 100 | 100 | 100 |
| NSP1\_protein | 99.66 | 100 | 95.83 | 98 |
| NSP10\_protein | 99.66 | 100 | 99.55 | 100 |
| NSP12\_protein | 99.66 | 100 | 100 | 100 |
| NSP13\_protein | 99.66 | 100 | 100 | 100 |
| NSP14\_protein | 99.66 | 100 | 100 | 100 |
| NSP15\_protein | 99.66 | 100 | 100 | 100 |
| NSP16\_protein | 99.66 | 100 | 100 | 100 |
| NSP2\_protein | 99.66 | 100 | 100 | 100 |
| NSP3\_cd21525\_SUD\_C\_SARS-CoV\_Nsp3 | 99.66 | 94.62 | 99.19 | 97 |
| NSP3\_cd21557\_Macro\_X\_Nsp3-like | 99.66 | 100 | 100 | 100 |
| NSP3\_cd21717\_TM\_Y\_SARS-CoV-like\_Nsp3\_C | 99.66 | 100 | 99.19 | 100 |
| NSP3\_cd21732\_betaCoV\_PLPro | 99.66 | 100 | 100 | 100 |
| NSP3\_cd21822\_SARS-CoV-like\_Nsp3\_NAB | 99.66 | 98.32 | 98.32 | 98 |
| NSP3\_cl00019\_Macro\_SF | 99.66 | 100 | 97.62 | 99 |
| NSP3\_cl13138\_SUD-M | 99.66 | 99.17 | 96.77 | 98 |
| NSP3\_cl13772\_DUF3655 | 99.66 | 100 | 100 | 100 |
| NSP5\_protein | 99.66 | 100 | 100 | 100 |
| NSP7\_protein | 99.66 | 100 | 100 | 100 |
| NSP8\_protein | 99.66 | 100 | 100 | 100 |
| NSP9\_protein | 99.66 | 98.22 | 100 | 99 |
| orf3a\_protein | 99.66 | 100 | 96.67 | 98 |
| orf7a\_protein | 99.66 | 100 | 92.31 | 96 |
| orf8\_protein | 99.66 | 95 | 100 | 97 |
| orf9b\_protein | 99.66 | 100 | 100 | 100 |
| S\_protein | 99.66 | 100 | 100 | 100 |

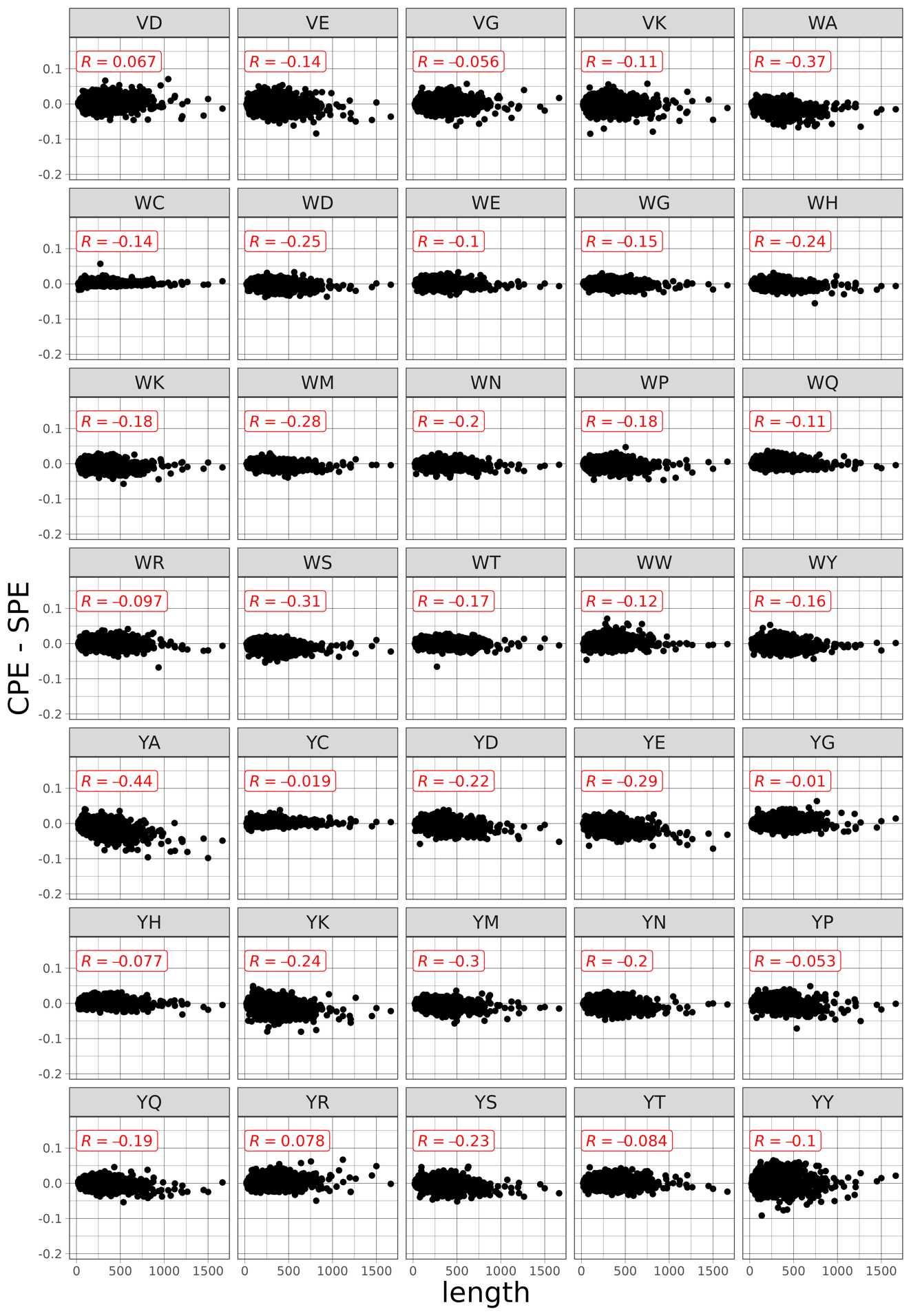
A screenshot of a graph

Description automatically generated

**Fig. S1** | The scatter plots of the the difference in energy estimates (from sequence and structure) and protein length across all 210 pairwise interactions, along with the correlation coefficients between these differences in energy estimates and protein length for each of the 210 pairwise interactions.



**Fig. S1** | (continued)



**Fig. S1** | (continued)

A screenshot of a graph

Description automatically generated

**Fig. S1** | (continued)

A graph of numbers and letters

Description automatically generated with medium confidence

**Fig. S1** | (continued)

A chart of numbers and letters

Description automatically generated with medium confidence

**Fig. S1** | (continued)



**Fig. S2 |** The Clustering analysis of spike glycoprotein structures from SARS-CoV, SARS-CoV-2, and MERS-CoV based on CPE method.



**Fig. S3 |** The Clustering analysis of spike glycoprotein structures from SARS-CoV, SARS-CoV-2, and MERS-CoV based on SPE method.



**Fig. S4 |** The Clustering analysis of spike glycoprotein structures from SARS-CoV, SARS-CoV-2, and MERS-CoV based on TM-Vec method.



**Fig. S5 |** The Clustering analysis of spike glycoprotein structures from SARS-CoV, SARS-CoV-2, and MERS-CoV based on MSA method.



**Fig. S6 |** **UMAP Visualization of Energy Profiles in Large-Scale SARS-Cov2 data set.** The UMAP projection of Structural Energy Profiles (SPE) on 28 protein families with a total of 4,405 protein models. UMAP plot was generated using parameters n\_neighbors = 150 and min\_dist = 0.1.



**Fig. S7 |** **UMAP Visualization of Energy Profiles in Large-Scale SARS-Cov2 data set.** The UMAP projection of Compositional Energy Profiles (CPE) on 28 protein families with a total of 4,405 protein models. UMAP plot was generated using parameters n\_neighbors = 150 and min\_dist = 0.1.



**Fig. S8 |** **UMAP Visualization of Energy Profiles in Large-Scale SARS-Cov2 data set.** The UMAP projection of TM-Vec on 28 protein families with a total of 4,405 protein models. UMAP plot was generated using parameters n\_neighbors = 150 and min\_dist = 0.1.