Supporting Information

Landscape-Based Mutational Sensitivity Cartography and Network Community Analysis of the SARS-CoV-2 Spike Protein Structures: Quantifying Functional Effects of the Circulating D614G Variant

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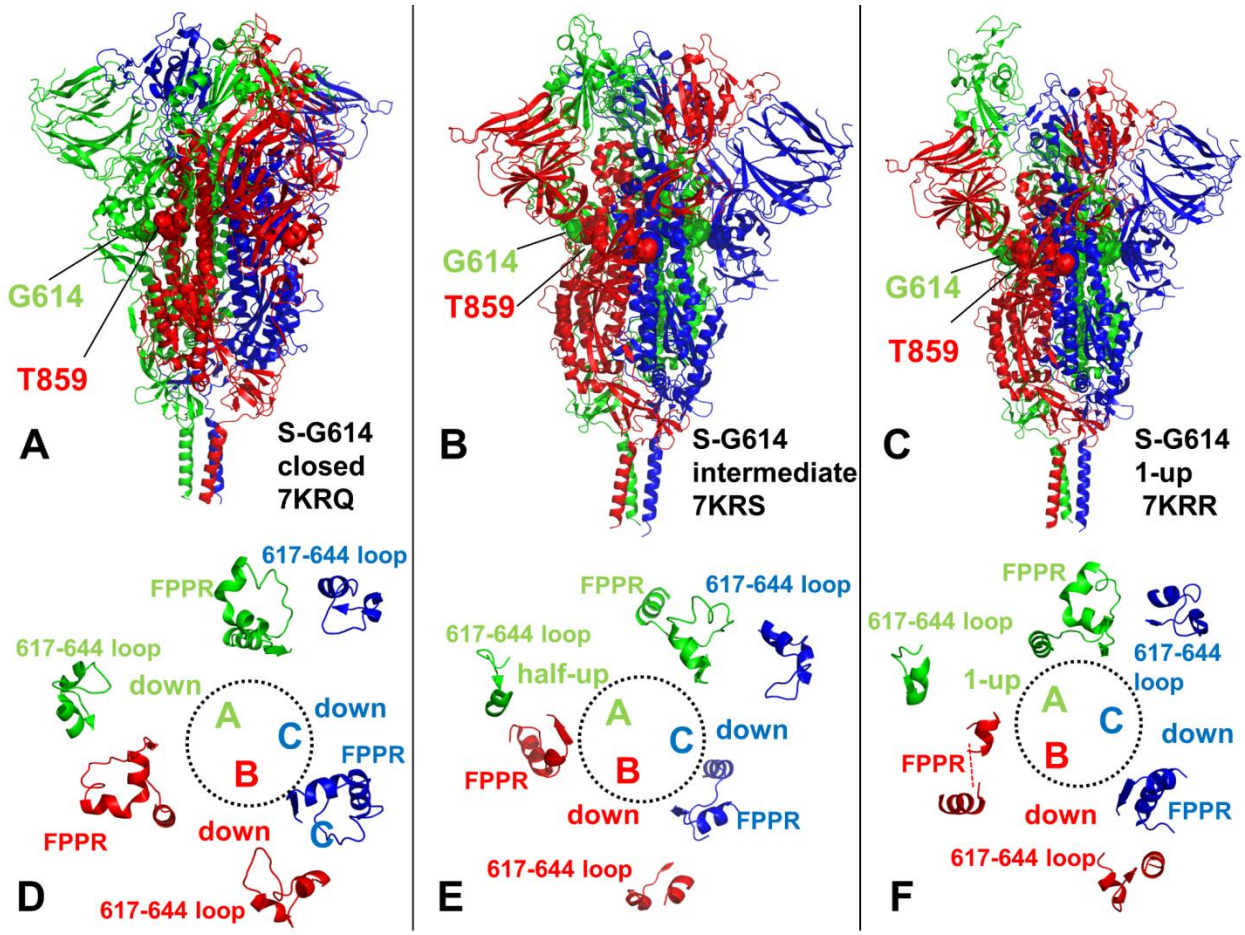

Figure S1. Cryo-EM structures of the SARS-CoV-2 S trimer structures used in this study. The cryo-EM structures of SARS-CoV-2 S-G614 in the closed state, pdb id 7KRQ (A), in the intermediate state, pdb id 7KRS (B) and 1 RBD-up open form, pdb id 7KRR (C). The structure is in ribbons with protomers A,B,C are colored in green, red and blue. The position of G614 and T859 are shown in spheres colored according to the chain. (D-F) Structures of the 630 loop (residues 617 to 644) and FPPR (residues 823 to 862) are shown for protomer A in green ribbons, protomer B in red ribbons and protomer C in blue ribbons.

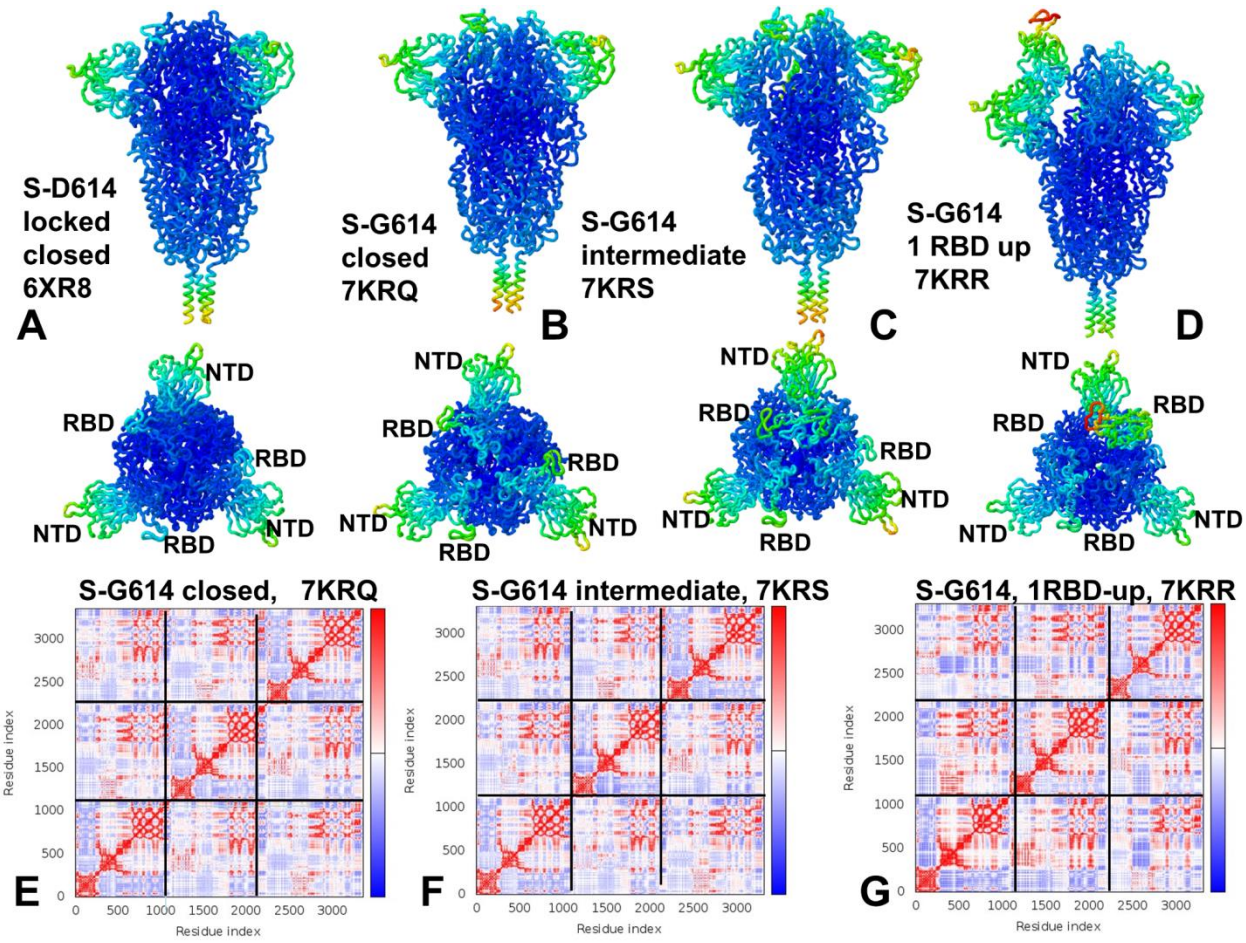

Figure S2. Conformational mobility profiles for the SARS-CoV-2 S-D614 trimer in the locked closed state, pdb id 6XR8 (A), SARS-CoV-2 S-G614 in the closed state, pdb id 7KRQ (B), in the intermediate state, pdb id 7KRS (C), and 1 RBD-up open form, pdb id 7KRR (D). The structures are shown in ribbons with the rigidity-to-flexibility scale colored from blue to red**.** The middle panel shows top views for the SARS-CoV-2 S-D614 structure (A) and SARS-CoV-2 S-G614 trimer structures in the locked, intermediate and open forms respectively (B-D). The covariance matrix of couplings between pairs of residues is shown for the SARS-CoV-2 S-G614 in the closed state (E), SARS-CoV-2 S-G614 in the intermediate state (F), and SARS-CoV-2 S-G614 in the 1 RBD-up open form (G). Cross-correlations of residue-based fluctuations vary between +1 (correlated motion; fluctuation vectors in the same

direction, colored in dark red) and -1 (anti-correlated motions; fluctuation vectors in the same direction, colored in dark blue). The values > 0.5 are colored in dark red and the lower bound in the color bar indicates the value of the most anti-correlated pairs. The boxes highlight cross-correlations for the protomer A, protomer B and protomer C.

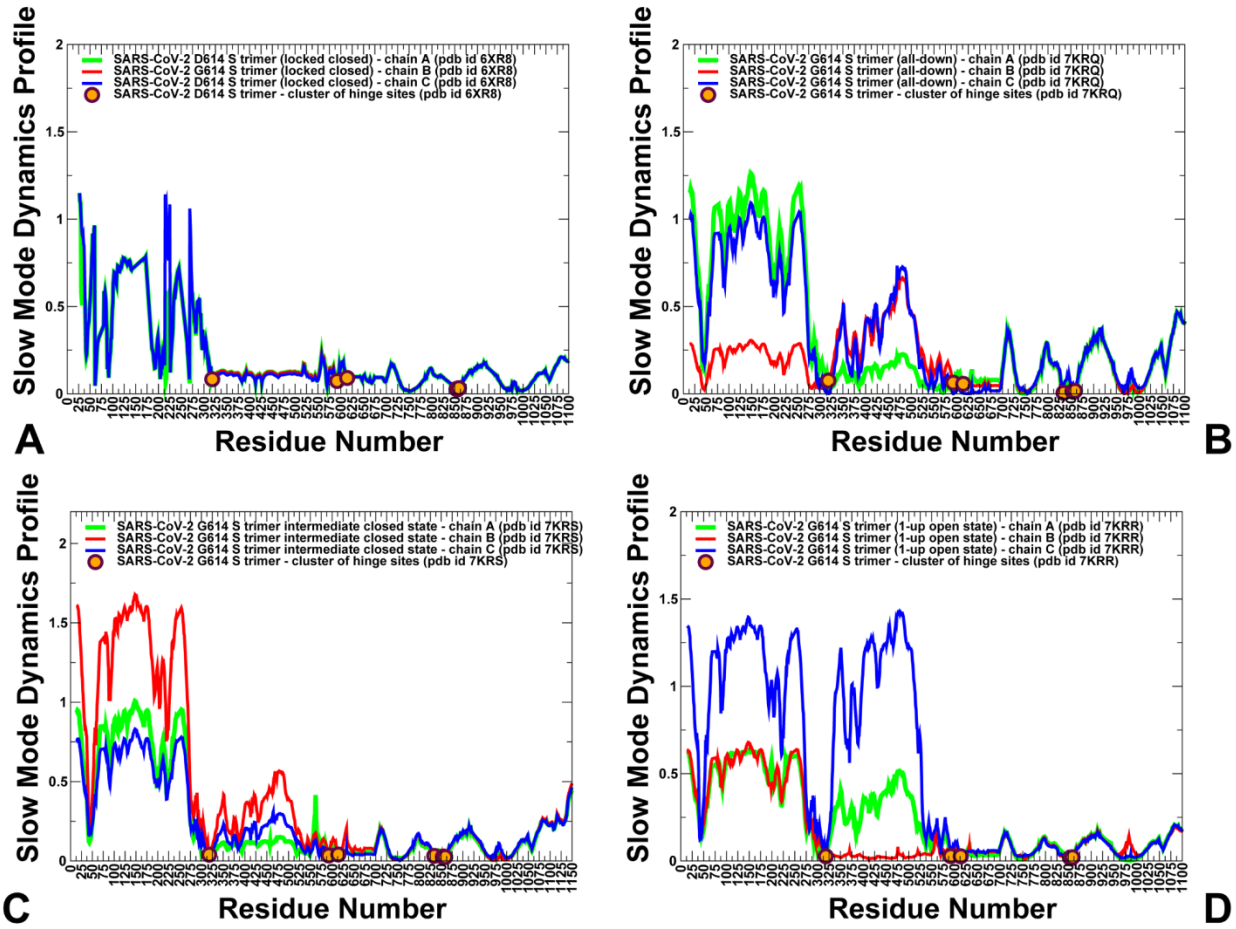

Figure S3. Functional dynamics of the SARS-CoV-2 S-D614 and S-G614 trimer structures in the locked closed, intermediate and open forms obtained using PCA of atomistic MD trajectories. The reported essential mobility profiles were averaged over the first three major low frequency modes. (A) The essential mobility profiles for the SARS-CoV-2 S-D614 in the locked closed form (pdb id 6XR8). (B) The slow mode profile for the SARS-CoV-2 S-G614 trimer structure in the closed form (pdb id 7KRQ). (C) The slow mode profile for the SARS-CoV-2 S-G614 trimer in the intermediate closed form (pdb id 7KRS). (D) The slow mode profile for the SARS-CoV-2 S-G614 trimer structure in the 1 RBD-up open form (pdb id 7KRS). The profiles for protomer chains A, B and C are shown in green, red and blue lines, respectively. The positions of the hinge sites forming the inter-protomer cluster F318, F592, D614/G614, Y855, I856, and T859 are shown along the profiles in filled orange-colored circles.

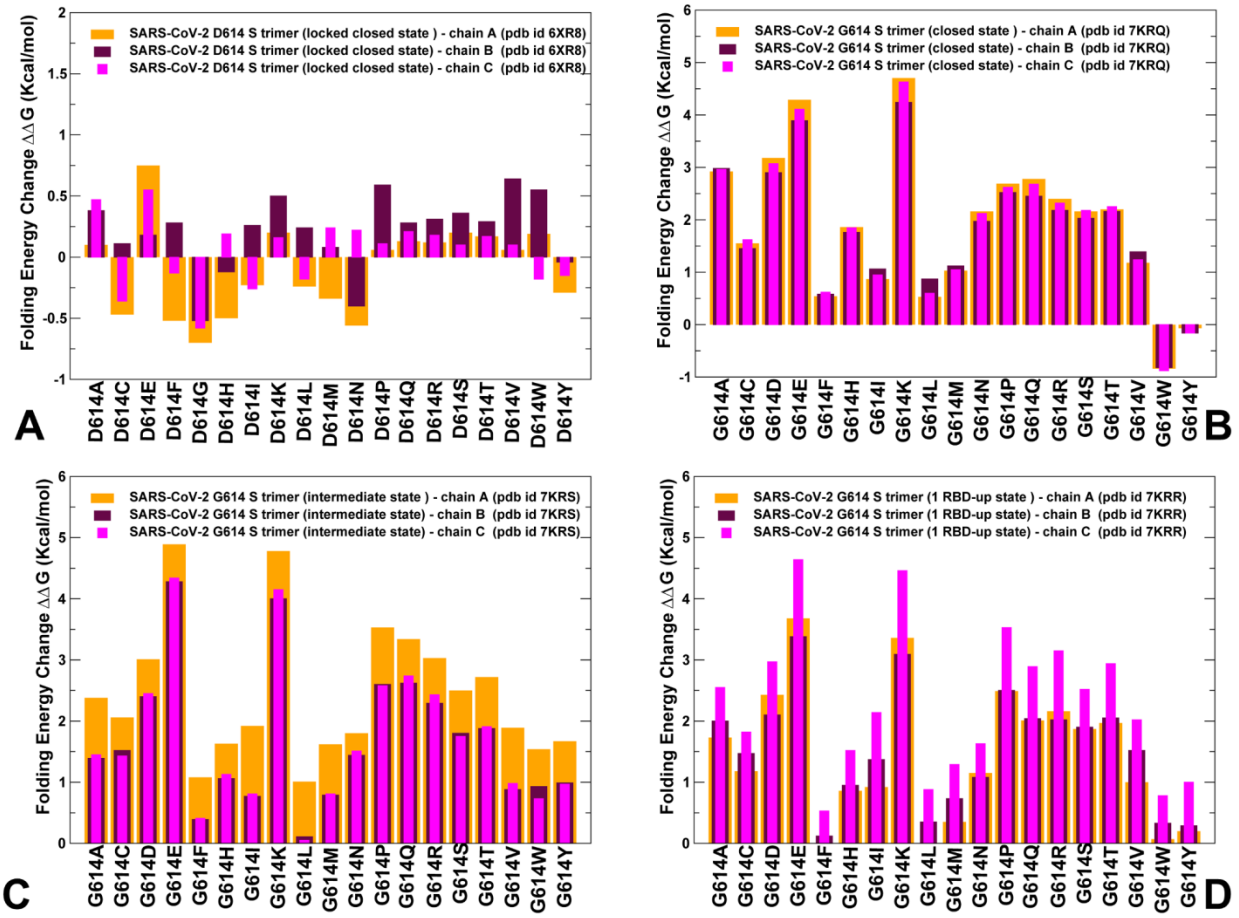

Figure S4. Mutational sensitivity analysis of the SARS-CoV-2 S-D614 and S-G614 trimers. Mutational sensitivity scanning of D614 position in the closed form of the S-D614 protein (A). Mutational sensitivity scanning of G614 position in the closed form of the S-G614 protein (B), intermediate state (C) and 1 RBD-up open state (D). The protein stability changes are shown for protomer A in orange-colored bars, for protomer B in maroon-colored bars, and for the protomer C in magenta-colored bars.