High Throughput Evaluation of SARS-Cov-2 Spike Protein Variants Using Conformational State Dynamics

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The COVID-19 pandemic has greatly affected individuals, families, health care systems, societies and the world economy. Whereas great advances have been achieved in record time, a lot remains to be learned about the infection mechanisms of its causative agent, the SARS-CoV-2 coronavirus. The SARS-CoV-2 Spike protein interacts with the human acetylcholinesterase 2 receptor as part of its entry mechanism. To do so, the receptor binding domain (RBD) of Spike needs to be in an open state conformation. Here we utilise coarse-grained normal mode analyses to model the dynamics of the SARS-CoV-2 Spike protein as well as the transition probabilities between open and closed conformations for the wild type and the D614G mutant as well other variants isolated experimentally. We proceed to perform several possible in silico single mutations of Spike, 17081 in total, to determine positions and specific Spike mutations that may affect the occupancy of the open and closed states. We calculate transition probabilities between the open and closed stated using the overlap of eigenvectors from one state to another. Transition probabilities are employed in a Markov model to determine state occupancies. Our results correctly model a shift in occupancy of the more transmissible D614G strain towards higher occupancy of the open state via an increase of flexibility of the closed state and concomitant decrease of flexibility of the open state. We utilize global vibrational entropy differences to select candidate single point mutations that affect the flexibility of the open and closed states and confirm the shift in occupancies for the most critical mutations. We predict the same effect seen in D614G for several mutations on Glycine residues (404, 416, 504, 252) as well as residues K417, D467 and N501, offering one possible explanation for the higher infectivity of the B.1.1.7, 501.V2 and P.1 strains. The specific mutations of Spike identified here, while still requiring experimental validation, may guide future studies to further our understanding of SARS-CoV-2. This is to our knowledge the first use of normal mode analysis to model conformational state transitions and the effect of mutations. These models can be used to search between a large number of possible mutations to predict future highly transmissible strains, guide future pharmacological research, and also guide public health decisions in the face of the emergence of new strains of coronavirus.