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Discovery of COVID-19 N-Protein Active Sites for Efficient Antiviral Drug Target Treatment: An Innovative Approach using Torsion Angle Changes in Relation to Functional Activity of Viral N-Proteins

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Abstract

COVID-19, a SARS-CoV-2 coronavirus originating from Southeast Asia, has resulted in 86.2 million cases and 1.87 million deaths worldwide. The COVID-19 N-protein is responsible for viral replication by assisting in viral RNA synthesis and attaching the viral genome to the replicase-transcriptase complex (RTC). Novel vaccine systems, such as live-attenuated and inactive vaccines, are aimed at suppressing the N-protein by blocking its active sites in domains involved in phosphorylation, oligomerization, and RNA binding. The purpose of this study was to determine the active sites of the COVID-19 N-protein for drug targets by identifying torsion angle classifiers for N-protein structural change with respective residues that determine N-protein functional activity.

In the study, angle classifiers with a minimum structural accuracy of 80% determined from NAMD simulation data were analyzed by Principal Component Analysis and cross-validated by Logistic Regression, Support Vector Machine, and Random Forest Classification. By removing residues through molecular dynamics, function-determining residues were found to be residue 189 for the phosphorylation domain and residues 252 and 375 for both the N-protein oligomerization and binding domains. Residues 252 and 375 not only were implicated in the aforementioned domains, but their respective torsion angles, psi 252 and phi 375, predicted N-protein structure with 100% accuracy. Additionally, the respective angles of residue 189, phi and psi 189, predicted N-protein structure with 90.7% accuracy. Future applications include virtual drug screening to test the accuracy of drug targets and determining active sites for COVID-19 S-Protein and ACE2 protein, proteins used to bind to and invade host cells.