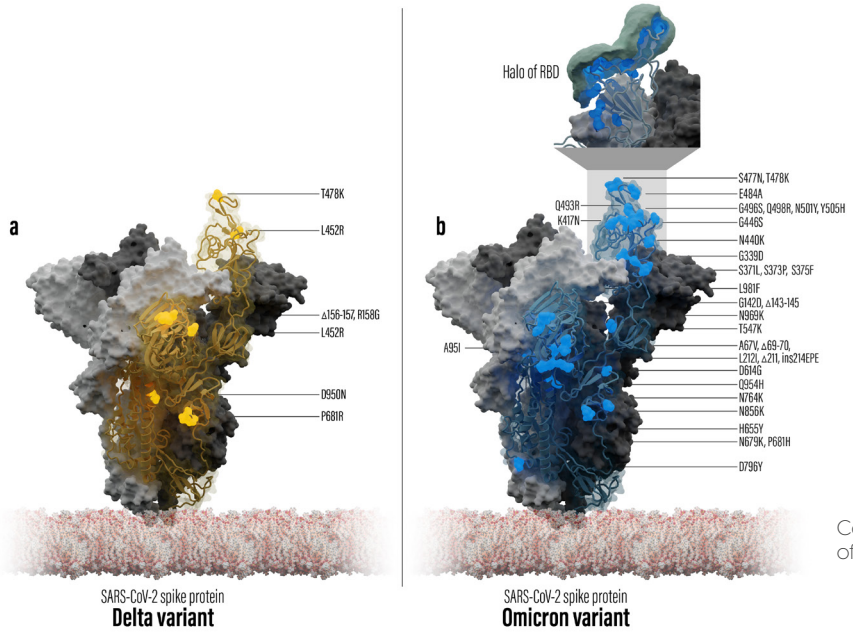


Comparison of mutation sites of Delta and Omicron variants.

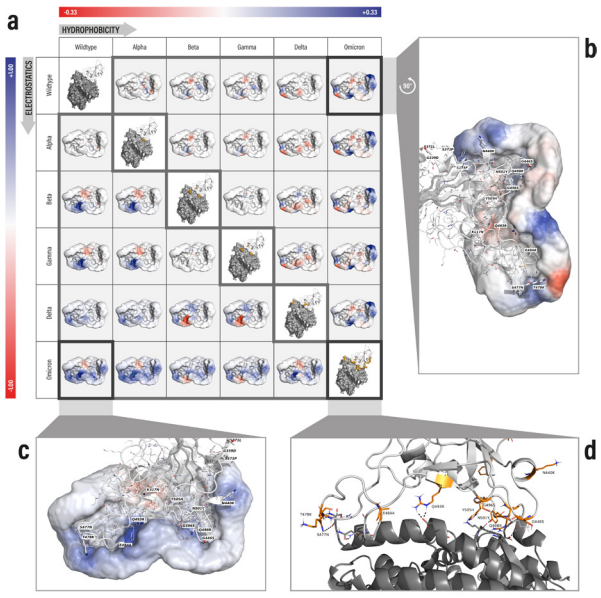
CASE STUDY | PROTEIN-PROTEIN INTERACTION

Binding **Affinity**

Our Halo technology was applied to study the influence of amino-acid exchanges on the affinity of the SARS-CoV-2 spike RBD to the human receptor hACE2. We developed and employed an empirical scoring function (ESF) closely related to the linear interaction energy (LIE) method, which is based on experimental binding data and molecular dynamics simulations.

Our analysis focuses on effects of observed amino acid exchanges. We analyzed the Halos of the wild-type and RBD variants. If the Halo comparison demonstrated a substantial change, we fed this variant into a LIE-based molecular dynamics modeling pipeline to predict the corresponding change in binding affinity.

This approach provides early structural insights and binding affinity estimates before experimental complex structures and experimental binding data will become available.



Surface representation of Halo difference point clouds targeting pairwise spike RBD comparisons.

a: Each Difference-Halo was calculated by subtracting Halo field values of the variant associated with column from Halo field values of the variant associated with row. Upper triangle: hydrophobicity difference Halos; Lower triangle: electrostatics difference Halos; Diagonal: binding interfaces of spike RBD variants in complex with hACE2

b: WT *vs.* Omicron hydrophobicity difference field.

c: WT *vs.* Omicron electrostatics difference field.

d: Omicron RBD-hACE binding interface revealing an additional hydrogen bond between residues Arg493 and hACE2 Glu35.

V. Durmaz, K. Köchl, A. Krassnigg, L. Parigger, M. Hetmann, A. Singh, D. Nutz, A. Korsunsky, U. Kahler, C. König, L. Chang, M. Krebs, R. Bassetto, T. Pavkov-Keller, V. Resch, K. Gruber, G. Steinkellner & C. C. Gruber *Sci Rep* **12**, 14534 (2022). https://doi.org/10.1038/s41598-022-18507-y.