Protein flexibility and glycan dynamics of the SARS-CoV-2 spike

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Spike protein of the SARS-CoV-2 mediates entry of the virus into human cells and is the main target of the vaccines. Spike surface is mostly hidden from the immune system behind a dynamic shield made of complex polysaccharides (glycans), which prevent antibody binding and complicate pharmacological interventions. Genetic variability of the virus leads to mutations in the exposed parts of the Spike and emergence of variants like Omicron, able to escape known vaccines. Keeping the advantage over the virus requires rational design of further vaccination strategies, which critically depends on accurate prediction of antibody binding sites that are accessible through the glycan shield and in the context of the whole virus.

To address these challenges, we combined structural biology data with bioinformatic predictions and constructed an atomistic model of four glycosylated spikes, which included viral membrane and explicit solvent, totalling at ~4M atoms. An aggregated 10 µs of molecular dynamics simulations was required to reveal the structural dynamics of the spike and its glycans. Simulations of this scale are only possible through access to a tier-0 supercomputer: in our case thanks to a generous priority allocation of 20M cpu hours at the SuperMUC supercomputer in Germany.

Combining results of the simulations with cryo-electron tomography of whole virions, we revealed surprising flexibility of the heavily glycosylated spike protein. We have also predicted several new antibody binding sites which can be used to design novel vaccines. Beyond SARS-CoV-2, the workflow is applicable to all enveloped viruses as well as other pathogens. Our work demonstrates how large scale computer simulations can help with great societal challenges like the pandemic.