Motions of the activated spike protein

Conformational plasticity of the spike protein S

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In Short

- Protein structure and dynamics
- Molecular modeling of protein activation
- Lipid-protein interactions in protein function
- Dynamic hydrogen bonds in protein function

Spike protein S of SARS-CoV-2 mediates virion entrance by binding to a membrane receptor of the host cell. This makes description of the motions of protein S a key step towards understanding early events during interactions of the virion with a host cell. Research planned here aims to use computational approaches to derive an atomistic description of the motions of protein S activated via proteolytic cleavage.

Protein S is a homotrimer of three protein chains anchored in the membrane (Fig. 1). The protein is heavily glycosylated, and its activation involved proteolytic cleavage. Research planned here is focused on deciphering how glycosylation influences protein motions, and on the conformational dynamics of protein S at early stages following proteolytic cleavage.

The large size of protein S makes it difficult to sample efficiently protein motions at the atomic level of detail. To circumvent this difficulty, in a first approximation we will study the conformational dynamics of protein S by using only the soluble ectodomain of the protein (Fig. 2). Preliminary computations have indicated the protein has flexible regions; to sample adequately the motions of protein S, the supercomputing resources of the HLRN are essential.

All molecular dynamics simulations will be performed using standard approaches. Briefly, the soluble protein is first placed in a box of water molecules - in the case of a membrane protein, it will be embedded in a hydrated lipid membrane environment. Ions are added for charge neutrality or to model a particular ion concentration. Interactions between atoms of the system are described by an equation that gives the potential energy of the system as a sum of terms for bonded and non-bonded interactions. Classical mechanical equations describing atom motion are solved numerically. The molecular dynamics trajectory obtained contains the coordinates of each atom of the system as a function of the simulation time, which here will extend to hundreds of nanoseconds. Here, simulations will be performed using the CHARMM force field equation [5]. and the NAMD simulation package [6].

Once generated, the molecular dynamics trajectory of a protein is subjected to analyses to characterize, for example, preferred protein conformations, or to identify interactions that govern protein conformational dynamics. These interactions can then be further probed by modeling mutants of the protein. In work planned here, hydrogen-bond clusters with potential role in shaping protein conformational dynamics will be identified with the Bridge software [4].

Computations presented above on the ectodomain of protein S will be augmented by work towards models of full-length protein S at particular steps of its reaction cycle. Preliminary tests with a lipid bilayer (Fig. 3.) composed of lipids

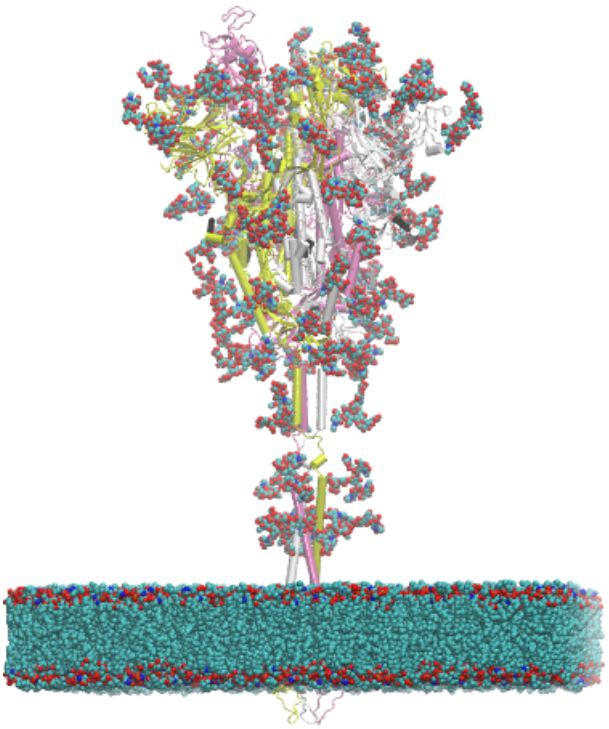

***Figure 1:** Illustration of protein S in the membrane based on the model of full-length protein S in pre-fusion conformation modeled in ref. [1] based on the structure solved experimentally in ref. [2]. The protein is shown as cartoons, with protein chains colored pink, yellow, and white. Glycosylation is shown with sugar moieties in van der Waals representation with carbon atoms colored cyan and oxygen, red. The proteolytic cleavage sites are colored black. All molecular graphics were prepared with Visual Molecular Dynamics, VMD [3].*

as recommended in ref. [1] indicated the bilayer could indeed be used to simulate the dynamics of membrane-anchored protein S.

Research planned here will provide molecular models of the ectodomain of protein S and of the full-length protein S, and of their conformational dynamics during early steps of the reaction coordinate of protein S. Efficient data analyses of intramolecular interactions of protein S will be performed with Bridge.

WWW

http://www.physik.fu-berlin.de/en/einrichtungen/ag/ag-bondar/

More Information

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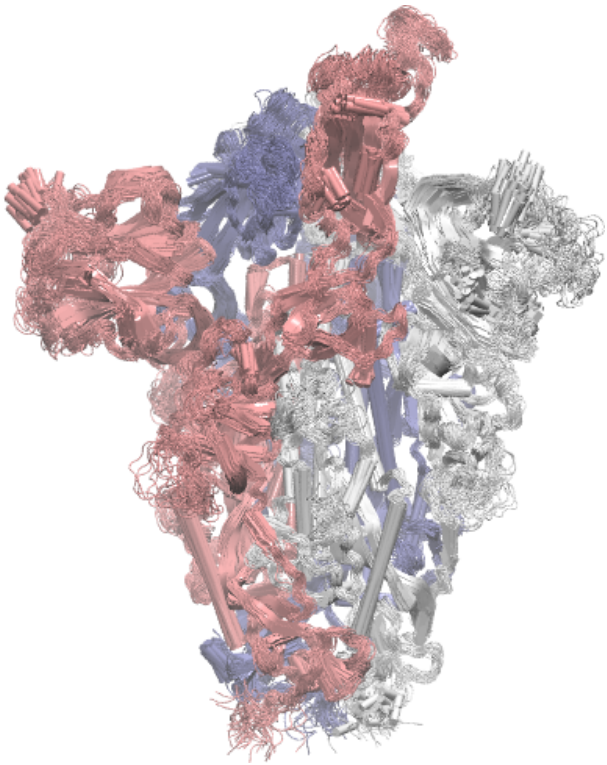

Figure 2: *Molecular graphics illustrating motions of the ectodomain of protein S. The images depicts three coordinate snapshots from an atomistic simulation of protein S in a box of water molecules. Loop regions of the protein are flexible during the simulations. Overall, the structure of the core of the protein is well preserved. For simplicity, sugar moieties, waters, ions, and hydrogen atoms are not shown.*

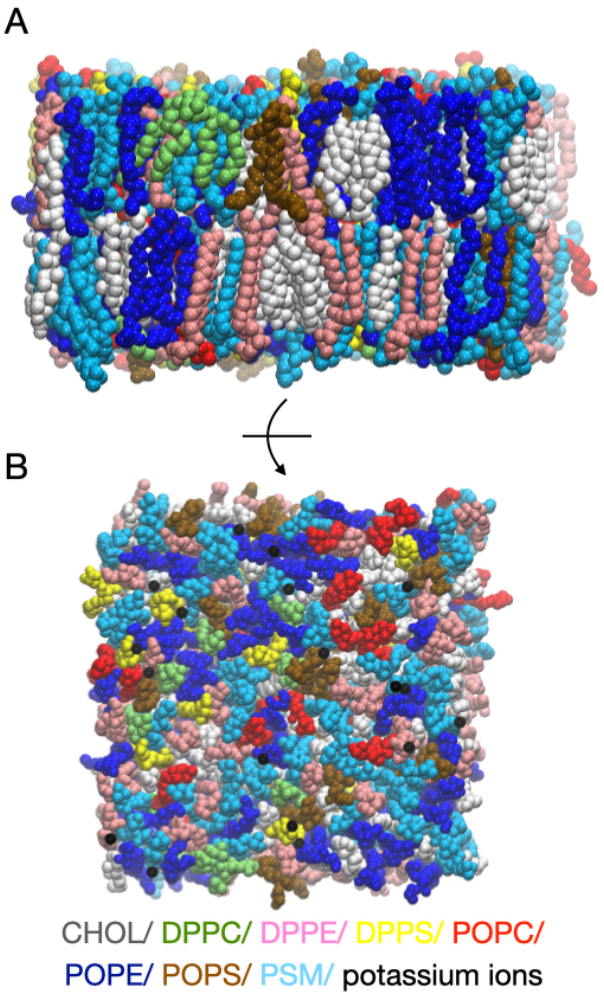

Figure 3: *Illustration of a lipid bilayer that models features of a viral membrane. The hydrated membrane patch was generated using a lipid composition as suggested in ref. [1].*

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