Electronic Supporting Information for "Interaction between SARS-CoV-2 spike glycoprotein and human skin models: a molecular dynamics study"

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1 Further details for MD Simulations

1.1 MD simulation parameters

In all simulations reported in Table 1 of the main paper the equations of motion were integrated with a 2 fs time step and electrostatic interactions were updated every 4 fs. All bonds between heavy atoms and hydrogen atoms were kept rigid. In all simulations we employed periodic boundary conditions in all directions. Lennard-Jones interactions were computed with a cutoff of 1.2 nm and switching function starting at 1.0 nm. Electrostatic interactions were computed using Particle Mesh Ewald (PME) algorithm using a real space cutoff set at 1.2 nm and a PME grid at 1.0 Å.

The temperature was set at 305K in all simulations employing the Langevin thermostat with a damping coefficient of 1 ps $^{-1}$. In NPT simulations we employed a Nosé-Hoover isotropic barostat with an oscillation period of of 50 fs and a damping time of 25 fs.

1.2 Preparation and Equilibration of the SC bilayer model

An atomistic model for a single bilayer membrane of the stratum corneum (SC) lipids with equimolar composition was built using the Input Generator module Membrane Builder[1] of CHARMM-GUI[2–4]. The initial SC structure had a surface with dimensions 24.01 x 24.01 nm^2 and a thickness of 8.5 nm including hydration water molecules. This structure was equilibrated following the standard CHARMM-GUI protocols of minimization and thermalization. A further equilibration NPT run was performed, until the bilayer area was stabilized, requiring a total of 10.73 ns. In order to obtain a SC bilayer structure suitable for our subsequent simulations, we remove all the hydration water molecules from the final configuration. The obtained dry bilayer is shown in Figure 3a and it was used as starting point for two subsequent simulations involving wetting of SC and interaction of SC with S protein, SC-W and SC-S as described in the Methods section of the main paper.

1.3 Preparation and Equilibration of the sebum layer model

The force field parameters for the three kinds of lipids molecules conforming the sebum (see main paper) were obtained using the Input Generator module Ligand Reader and Modeler[5] of CHARMM-GUI. Coordinate, topology and parameters files employed for these three sebum lipids are available for download[6]. An initial bulk system for the simulation of sebum was build using the "Input Generator" module of CHARMM-GUI. The initial sebum structure is a cubic box of 5 nm in length containing 42 molecules of triglyceride tri-cis-6-hexadecenoin, 22 molecules of lauryl palmitoleate and 10 molecules of squalene. The system was minimized and thermalized following the standard CHARMM-GUI protocols. The resulting bulk sebum structure had a liquid-like appearance in sharp contrast with the bilayer structure adopted by the SC lipids. In order to obtain a sebum system with the correct density, a further NPT simulation was performed with a total of 110 ns. The density of the obtained sebum system is 882±5 kg·m^{-3}. This value is slightly smaller than that of other previous MD sebum models[7] because in our sebum composition we included squalene (absent in the previous model) which has a smaller density.

The resulting equilibrated sebum system was too small for our subsequent simulations, particularly for the adsorption of the S protein, so we constructed a bigger system by replicating its molecules in the three directions. The dimensions of the resulting sebum surface (shown in Figure 3b) were $23.34 \times 23.34 \times 8.9\text{nm}^3$.

1.4 Preparation and Equilibration of the POPC bilayer model

Alternatively, atomistic simulations of a POPC bilayer were made in order to show whether the interaction of the S protein with the SC lipid matrix is analogous to other bilayers.

The POPC bilayer was prepared using the Input Generator module Membrane Builder of CHARMM-GUI. The initial POPC structure had the same dimensions than the initial SC structure (a surface with dimensions 24.01 x 24.01 nm^2 and a thickness of 8.5 nm including hydration water molecules). The constructed system contains 844 POPC molecules per leaflet.

As in the case of SC lipid system, this structure was equilibrated following the standard CHARMM-GUI protocols of minimization and thermalization. A further equilibration NPT run was performed, until the bilayer area was stabilized, requiring a total of 10.0 ns. In order to obtain a SC bilayer structure suitable for our subsequent simulations, we remove all the hydration water molecules from the final configuration.

2 Results for POPC system

Figure 1 shows the initial and final configuration of the spike glycoprotein onto a POPC bilayer. The similarities with the snapshots reported for the SC case in the main paper are clear. In Figures 2, 3 and 4 we report the same quantitative analysis for the spike - POPC bilayer as done in the main paper (RMSD, number of contacts and number of hydrogen bonds). For the sake of comparison, we also include the data for sebum and SC bilayer also reported in the main paper. The similarities between the POPC and SC results are clear, indicating the spike - lipid bilayer interaction does not significantly depends on the exact composition of the bilayer.

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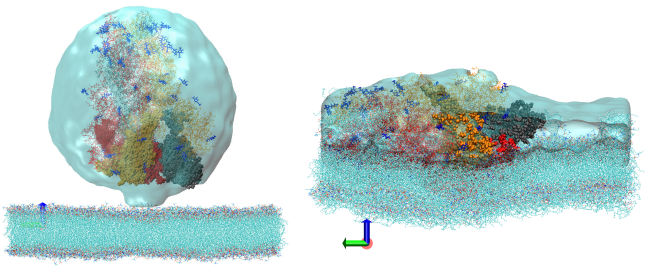

Fig. 1 Initial and final configuration of POPC bilayer and spike protein.

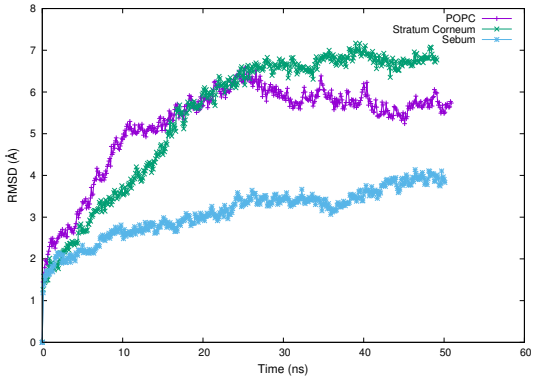

Fig. 2 RMSD for POPC simulation in comparison with SC lipids and sebum system.

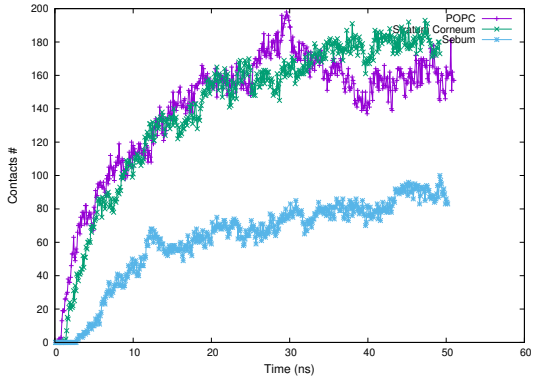

Fig. 3 Evolution of the number of contacts for POPC simulation in comparison with SC lipids and sebum system.

3 SMD simulations: perturbation of the adsorbed state of S onto Sebum

In the main paper, we report the results for the adsorption of S onto sebum (simulation SB-S, Table 2). The results reported in the main paper show that the S protein adsorbs over the sebum surface with an orientation close to its original perpendicular orientation (the original orientation was chosen as the one expected from the insertion of S in a viral membrane).

In order to study the stability of the obtained adsorbed state of S onto Sebum, we have performed additional Steering Molecular Dynamics (SMD) as implemented in NAMD[8]. In these SMD simulations, the Spike glycoprotein was pulled in a direction perpendicular to its vertical axis. The selected group of atoms that were steered were the ones belonging to residues 1070 to 1146, which are located opposite to the surface. A perturbation over these residues will make the protein tilt, allowing us to test the stability of the orientation of the protein (with its long axis nearly perpendicular to the surface). We report here results for pulling in two different directions, in the y axis and in the x axis (see snapshots in Figure 5). We selected two perpendicular directions because the protein is not isotropic (as can be seen in the two snapshots of the same initial configuration in Figure 5, taken from different views). Therefore perturbations in these directions may have different protein responses. In both cases, the pulling velocity was 50 nm/ns. We selected this velocity after tentative short simulations trying different values. In these trial simulations, we observed that larger pulling velocities induced deformation and denaturation of the protein without inducing detachment or tilt. In order to speed up the calculations, we selected a fast velocity for which protein denaturation was not observed. To ensure the requested velocity in SMD, a force constant of 50 kcal/mol/Å^2 was employed. The tilt angle was calculated as described in the subsection "Analysis of results" in the main paper. After the SMD simulations, the recovery of the system was analyzed by performing standard MD simulations starting from the last configuration of the SMD simulations using the same methodology as in the SB-S simulation.

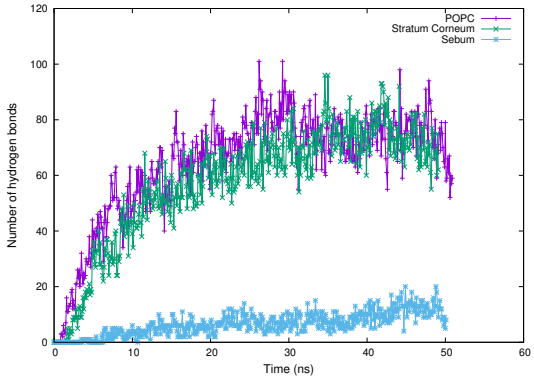

Fig. 4 Evolution of the number of hydrogen bonds for POPC simulation in comparison with SC lipids and sebum system.

The results for the SMD simulation with the external bias in the y direction are shown in Figure 5a (snapshots of this simulation are shown in Figure 5c). The tilt angle increased linearly with time from the initial value of ~ 16. We stopped the simulation when a tilt angle of $\sim$35º was reached ($\sim$60 ps). The recovery of the system after this perturbation is shown in Figure 5b. The tilt angle decays to ~ 20 after ~ 4 ns, close to the initial orientation, experiencing fluctuations for the remaining of the MD simulation. In the case of the perturbation in the x direction, the results were shown in Figure 5d (SMD perturbation) and Figure 5e (MD recovery). The pulling velocity was applied until a tilt angle similar to that obtained in the previous case ($\sim$35º) was reached. In this case, the SMD simulation required 95 ps as compared with the $\sim$60 ps required before (compare Figure 5a and Figure 5b). The recovery from the perturbation (Figure 5e) is similar to that ob-

tained in the previous case, although the final tilt angle is slightly larger.

These results indicate that the S protein adsorption onto sebum in the SB-S simulation is stable, and we do not expect a transition to a parallel orientation as in the SC-S simulations. .

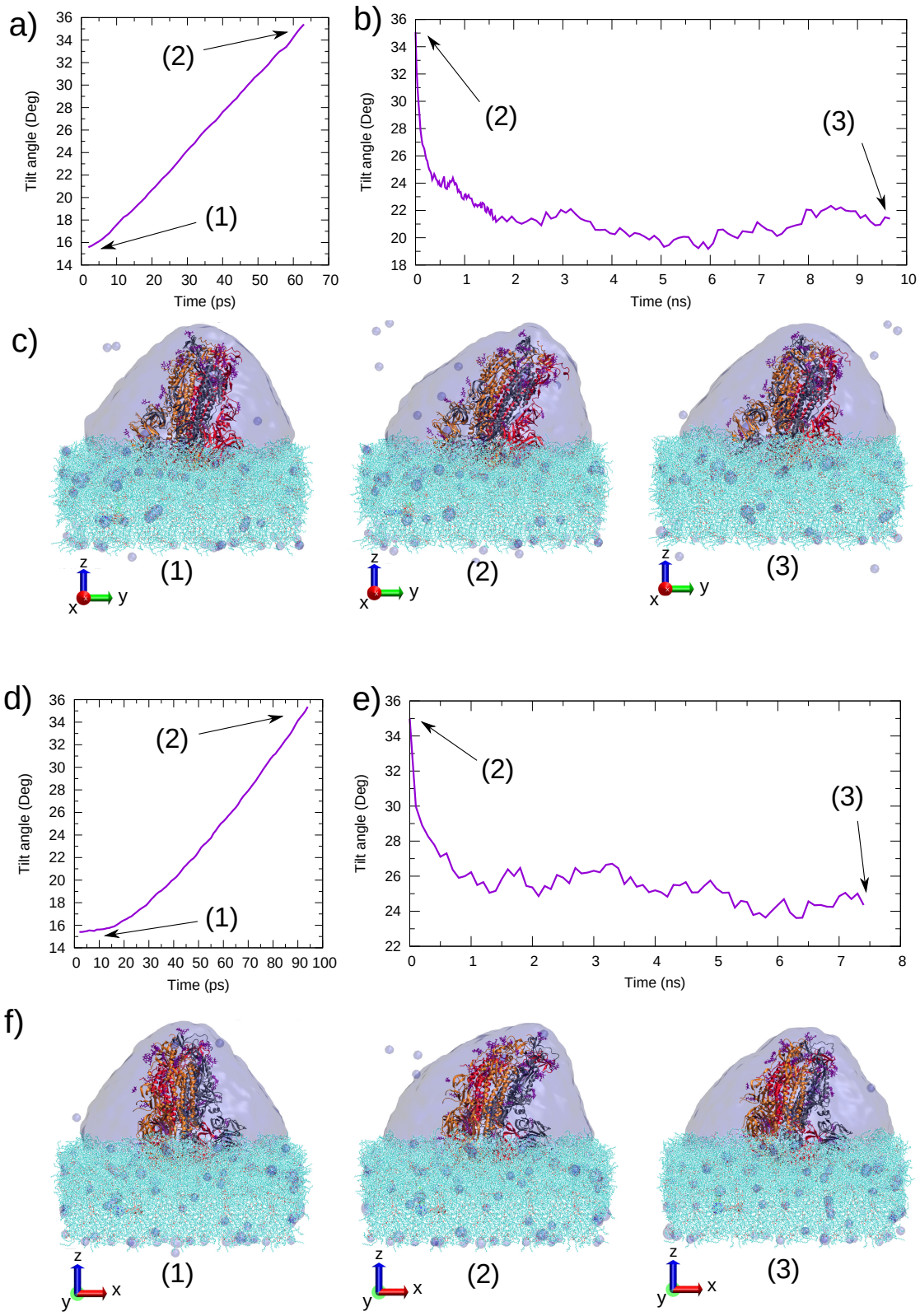

Fig. 5 Evolution of tilt angle in SMD and MD recovery simulations. a) Tilt angle as a function of time in SMD simulations pulling the S protein in the y direction; b) Tilt angle as a function of time in the MD recovery simulation after the SMD pulling in the y direction; c) Snapshots of the simulations corresponding to particular instants of time indicated in panels (a) and (b). Image 1 corresponds to the initial (adsorbed) configuration for SMD, image (2) corresponds to the final configuration for SMD and initial configuration for the MD recovery simulations and image (3) corresponds to the final configuration after recovery; d) Tilt angle as a function of time in the MD recovery simulation after the SMD pulling in the x direction; e) Tilt angle as a function of time in the MD recovery simulation after the SMD pulling in the x direction; f) Snapshots of the simulations corresponding to particular instants of time indicated in panels (d) and (e). Image 1 corresponds to the initial (adsorbed) configuration for SMD, image (2) corresponds to the final configuration for SMD and initial configuration for the MD recovery simulations and image (3) corresponds to the final configuration after recovery.

Notes and references

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