

Description of Additional Supplementary Files

File name: Supplementary Data 1

Description: Summary of the simulated structures and their links to GPCRmd.

File name: Supplementary Data 2

Description: Receptor breathing motions. Percentage of total frames identified as active, intermediate or inactive by the conformational analysis algorithm in each simulation.

File name: Supplementary Data 3

Description: Frequency (% of frames) of total lipid insertions in our simulated systems by receptor site (e.g.: TM3-TM4_{EC}).

File name: Supplementary Data 4

Description: Frequency (% of frames) of deep lipid insertions in our simulated systems by receptor site.

File name: Supplementary Data 5

Description: Insertions of lipid-like molecules found in experimental static structures.

File name: Supplementary Data 6

Description: Summary of all reported cases of lateral gateways identified through lipid insertions in the simulated systems.

File name: Supplementary Data 7

Description: Lipid insertion results for replication purposes. Please see README file for further details.

File name: Supplementary Data 8

Description: VMD sessions for all 3D structure figures presented in this paper.

File name: Supplementary Movie 1

Description: Lipid insertion into an allosteric pocket of the protease-activated receptor 2 (PAR2). This structure (PDB id: 5NDZ) was co-solved alongside an allosteric antagonist in its TM2-TM3-TM4_{IC} pocket. In our simulated apo systems of this structure, the pocket closes during equilibration without a ligand. However, as can be seen in the movie, a lipid insertion (cyan) occurs in this same pocket during its simulation. The native, co-solved ligand (green) has been superposed to better visualize the pocket. (GPCRmd id: [1018](#), trajectory id: 17251).

File name: Supplementary Movie 2

Description: Opening of a ligand gateway by a lipid insertion in Rhodopsin (lateral view). In this apo-system simulation, a lipid molecule (cyan) can be observed inserting deep into the rhodopsin (gray), reaching the ligand cavity itself. The retinal ligand originally co-solved in this structure, and absent in this apo form simulation, has been superposed in this video (green licorice) to help visualize the ligand cavity. Residues previously identified as potential gatekeepers (F1208^{5x43}, F273^{6x56}, and F276^{6x59}, see Fig. 4) appear in purple. PDB id: 5DYS, GPCRmd id: [872](#), trajectory id: 16264.

File name: Supplementary Movie 3

Description: Opening of a ligand gateway by a lipid insertion in Rhodopsin (apical view). Apical view of the same insertion described in **Supplementary Movie 2**. The lipid here is displayed in orange, the rhodopsin in gray and the superposed co-solved ligand in green. The insertion process is in this video observed from the extracellular side of the protein. PDB id: 5DYS, GPCRmd id: [872](#), trajectory id: 16264.