Supporting information to:

Open-Boundary Molecular Mechanics/Coarse-Grained Framework for Simulations of Low-Resolution G-Protein-Coupled Receptor-Ligand Complexes

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Figure SI 1

A scheme of the previous MM/CG implementation for the study of membrane protein/ligand complexes. In blue are the protein residues belonging to the MM region; in orange are those belonging to the interface *I*, while in black are the CG residues. The ligand is depicted in red. Atomistic water in the MM region is represented in ball and stick (red for O atoms and white for H atoms). The membrane and the hemisphere confining water molecules are represented as dashed lines.

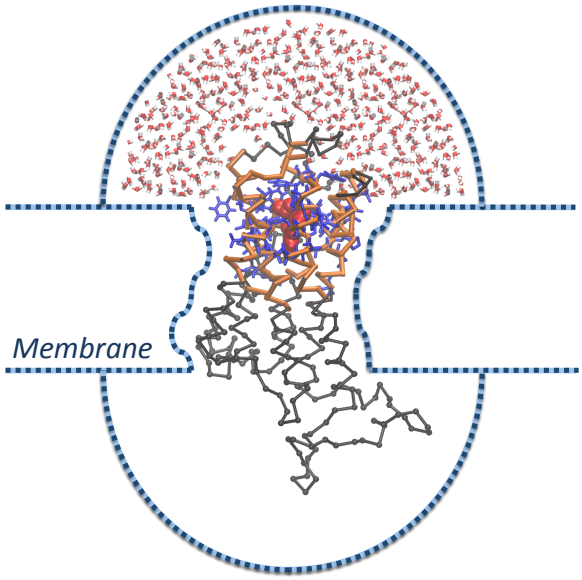


Figure SI 2

Radial density of water from the center of the MM_w region in OB-MM/CG simulation. The depletion of water molecules in the yellow-shaded area is due to the presence of the protein.

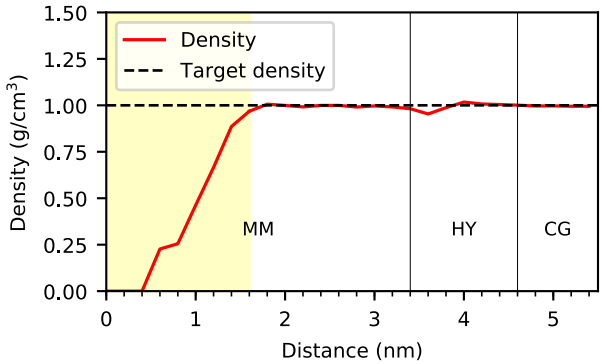


Figure SI 3

Structural and dynamical properties of water molecules in the all-atoms MD simulations are calculated in a hemispherical region (here represented within the dotted line) equivalent to the MM_w region of OB-MM/CG and MM/CG.

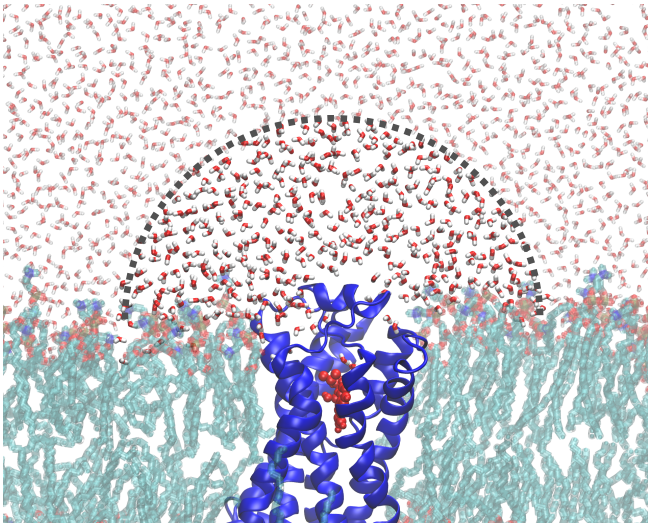


Figure SI 4

Oxygen-oxygen (**a**) and oxygen-hydrogen (**b**) radial distribution functions (RDFs) of the water molecules around the binding site in the all-atoms, MM/CG and OB-MM/CG simulations. Since our aim is to compare different approaches, the RDFs are not corrected for the excluded volume due to the protein. Water molecules closer than 1nm to the hemisphere in the MM/CG simulations are not taken into account in the computation.

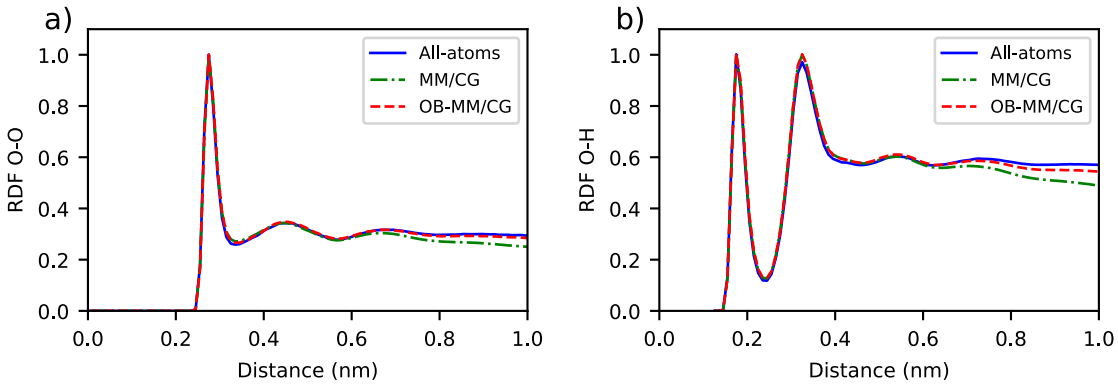


Figure SI 5

Snapshot of the binding site in the OB-MM/CG simulation overlapped with the X-ray structure (**a**,**b**, in red) and with a snapshot from the all-atoms simulation (**c**,**d**, in yellow). Residues forming hydrophobic interactions **(a**,**c)** or hydrogen bonds **(b**,**d)** with the ligand, as already observed in previous works[1-2], are represented in licorice along with the ligand.

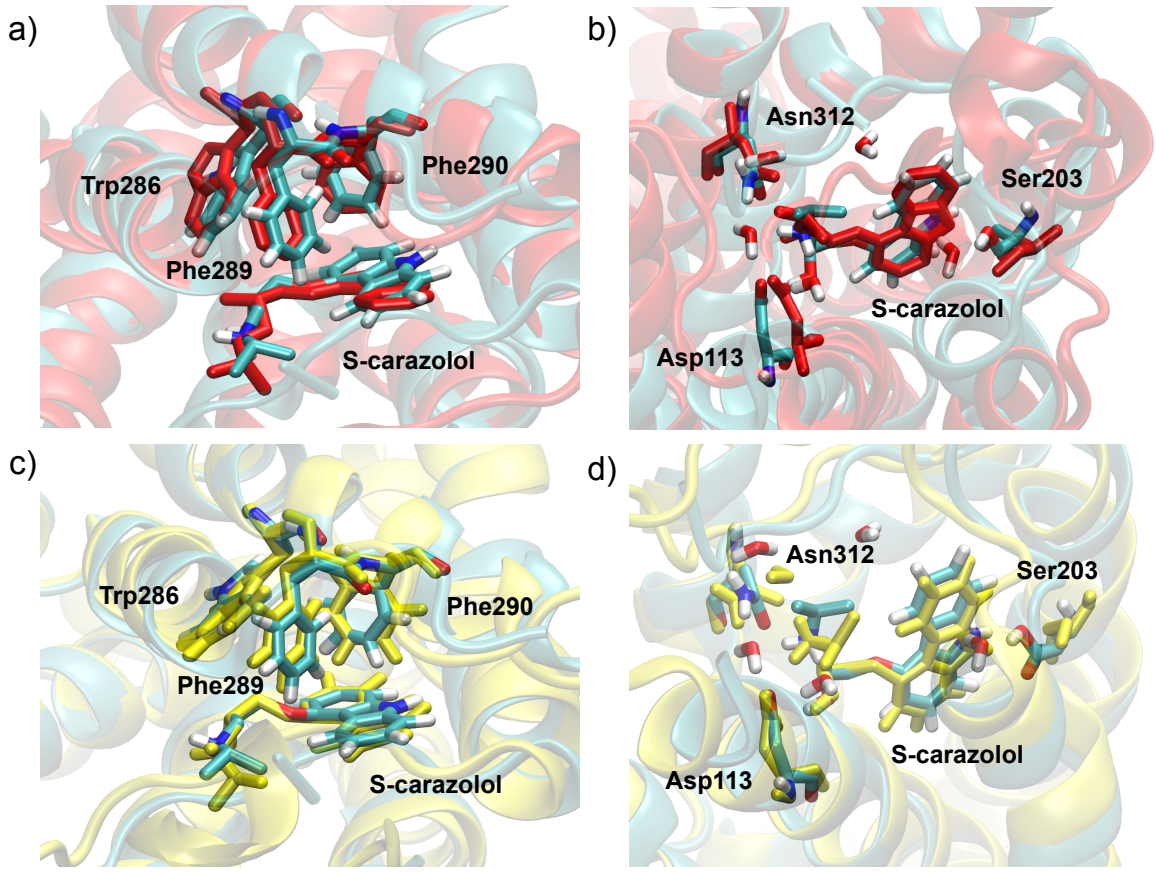
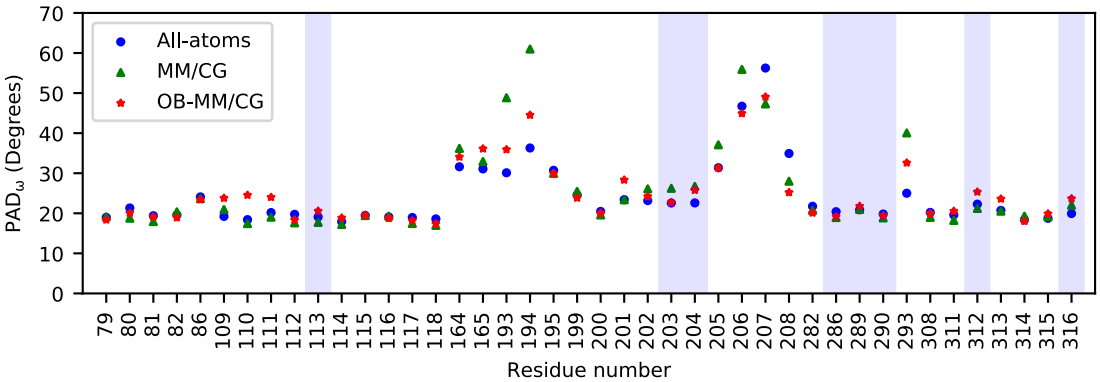


Figure SI 6

PAD_ω parameter, computed for the MM residues. PAD_ω is a function of the circular spread of the angle ω, given by the sum of ϕ and ψ Ramachandran angles, for each residue; it ranges from 0° (when ϕ and ψ dihedral angles do not change along the trajectory) to 180° (when ϕ and ψ assume random values). The blue-shaded areas correspond to the residues stabilizing the ligand through hydrophobic interactions or hydrogen bonds.



References

1. Chan, H. C. S.; Filipek, S.; Yuan, S. G. The Principles of Ligand Specificity on beta-2-adrenergic receptor. *Sci Rep-Uk* **2016,** *6*.
2. Vanni, S.; Neri, M.; Tavernelli, I.; Rothlisberger, U. Predicting Novel Binding Modes of Agonists to beta Adrenergic Receptors Using All-Atom Molecular Dynamics Simulations. *Plos Comput Biol* **2011,** *7* (1).