

SUPPORTING INFORMATION

Exploring Molecular Mechanisms of Ligand Recognition by Opioid Receptors with Metadynamics

Davide Provasi, Andrea Bortolato, and Marta Filizola

Contents:

| | |
|----------------|---|
| Table S1..... | 1 |
| Figure S1..... | 2 |
| Figure S2..... | 3 |
| Figure S3..... | 4 |

TABLE S1. Structural prediction of long intracellular loop regions of GPCRs with known crystal structure. The structural difference between IL2 and IL3 loop conformations predicted by fast *ab initio* loop prediction algorithms for globular proteins and corresponding regions in crystal structures is given in terms of C α RMSD (\AA) values.

| <i>ab initio</i> loop prediction algorithm | C α RMSD (\AA) | | | | |
|--|----------------------------------|-----------------------------|-------------------------------|-------------------------------|-------------------------|
| | Rhodopsin IL2 (13 residues) | Rhodopsin IL3 (23 residues) | β 2AR IL2 (12 residues) | β 1AR IL2 (12 residues) | AA2AR IL2 (13 residues) |
| | PDB ID | PDB ID | PDB ID | PDB ID | PDB ID |
| | 1GZM | 1GZM | 2RH1 | 2VT4 | 3ELM |
| Modloop | 12.0 | 19.2 | 7.9 | 11.0 | 4.8 |
| Dope | 8.6 | 6.0 | 9.6 | 6.9 | 6.9 |
| Loopy | 6.3 | 9.0 | 6.0 | 4.0 | 5.2 |
| Plop | 6.0 | 10.3 | 7.1 | 4.4 | 3.3 |
| Rosetta | 2.6 | 3.9 | 5.0 | 3.3 | 1.0 |

Abbreviations: AA2AR, adenosine A2A receptor; β 1AR, β 1 adrenergic receptor; β 2AR, β 2-adrenergic receptor; GPCRs, G-protein coupled receptors; IL, intracellular loop; RMSD, root mean square deviation; PDB ID, Protein Data Bank IDentification;

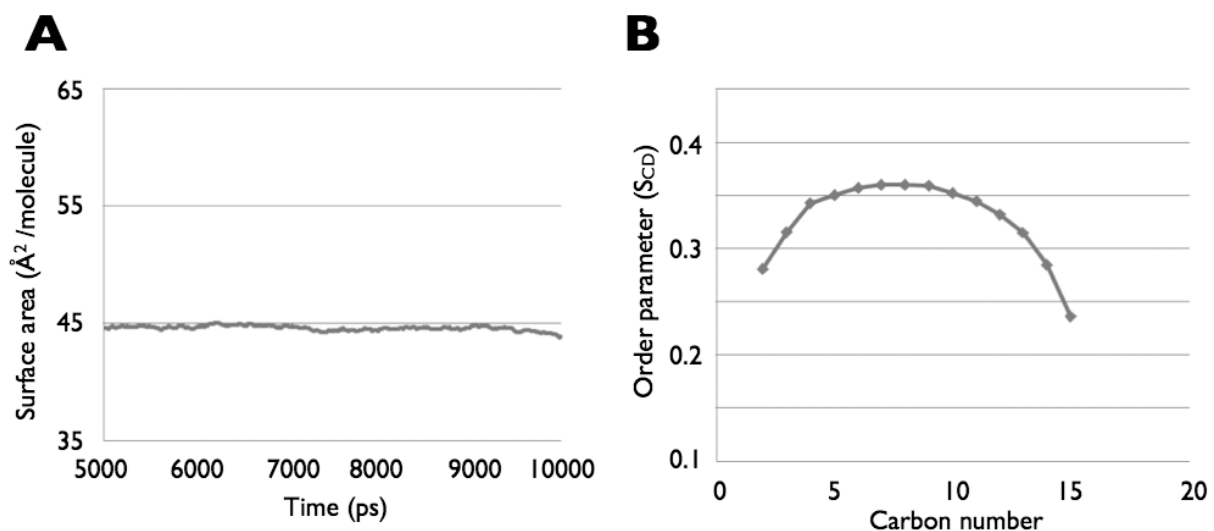


FIGURE S1 Dynamic behavior of the DPPC-20% cholesterol membrane environment during the last 5 ns of 10 ns MD simulations expressed as (A) surface area per lipid in the xy plane, and (B) deuterium order parameter profile.

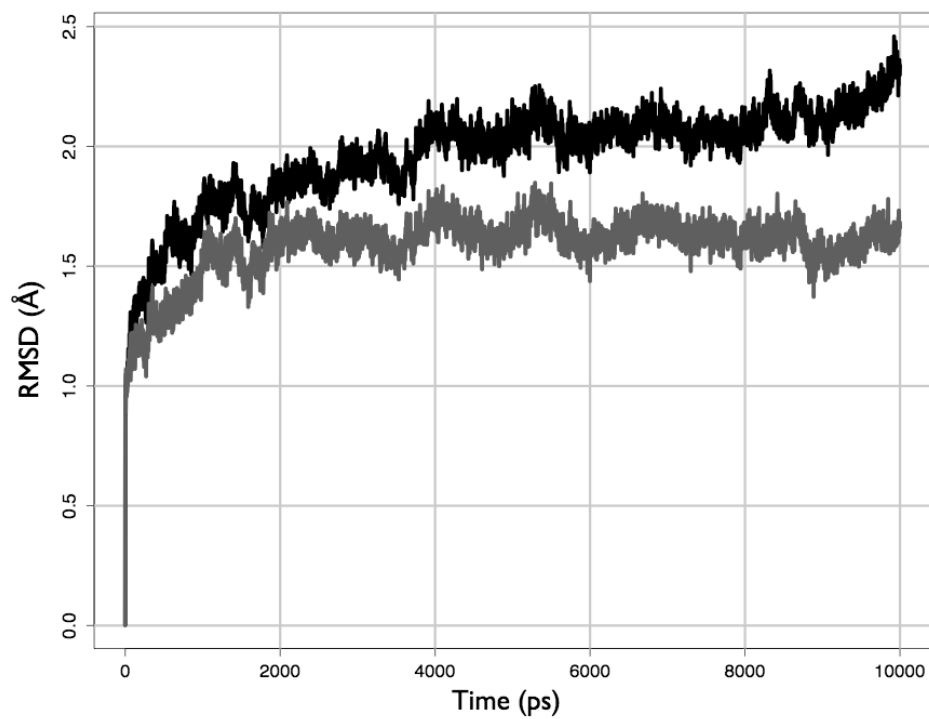


FIGURE S2. Time evolution of the backbone RMSD of human DOR (only TMs in grey and all atoms in black) during 10 ns unrestricted MD equilibration.

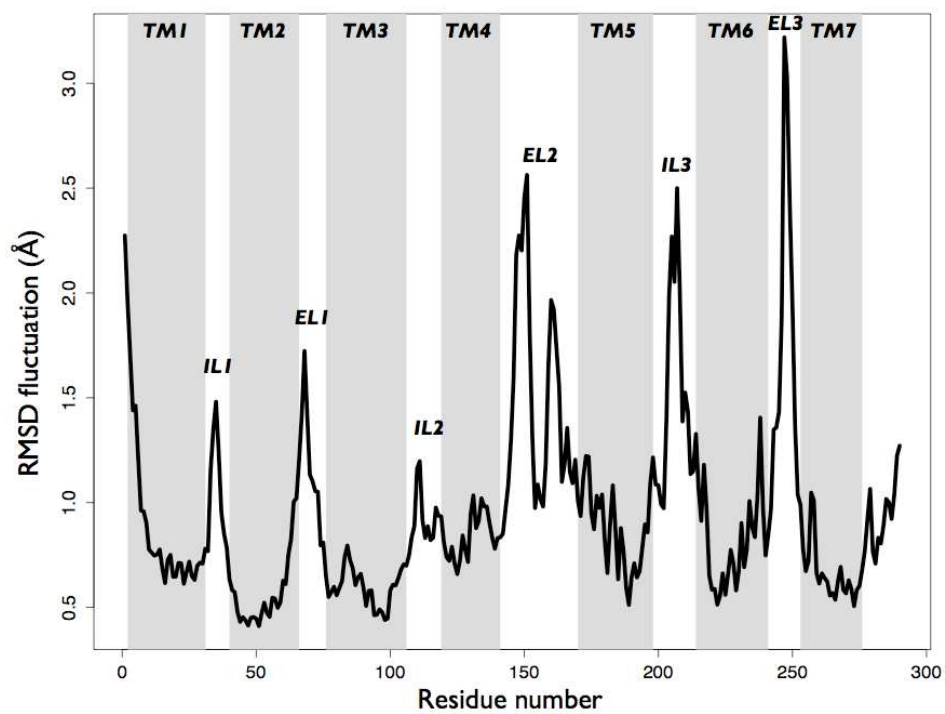


FIGURE S3. RMSD fluctuation per residue of human DOR during 10 ns unrestricted MD equilibration.