Effect of the lipidic membrane composition on the dynamical properties of the μ opioid receptor

Lipid rafts drifting in the membrane as an island in the ocean. Such structure, rigid and thick remains controversial because of its difficult experimental characterization [1]. Lipid rafts protect the protein of enzymes present in the memebrane and increase the effiency of signaling pathways. The protein/lipid interaction modulate protein conformations which condition their entry into lipid rafts.
Opioid receptors, whose structures were revealed in 2012, part of G-protein coupled receptors (GPCRs), are the target of **50 % of drugs on the actual market** [2]. The structural and functional properties of these transmembrane proteins are clearly affected by the lipid environment [3]. The hydrophobic mismatch promotes dimerization by reducing the entropy due to the adaptation of the membrane to protein [4]. Dimerization of μ protein involves different signaling pathways but are still poorly understood, as well as the presence of dimers in lipid rafts [5].

To analyze the influence of the lipid composition of the μ opioid receptor, molecular dynamics (MD) simulations, and coarse-grained models (MARTINI force fields) were chosen. Four lipids are compared: **DPPC** (1,2-dipalmitoyl phosphatidyl choline), **POPC** (1-palmitoyl-2-oleyl-sn-glycero-3-phosphocholine), **POPE** (1-palmitoyl-2-oleoyl-sn-glycero-3-phosphoethanolamine) and **cholesterol**.
Considering coarse-grained, simulations sizes have a lesser degree of accuracy than all-atoms but allow to understand the protein/lipid interactions differences from analyses of the thickness, the area per lipid, the tilt of the protein in the membrane, and the distance between amino acid and polar heads.
Ultimately, our goal is to perform MD simulations with **the most realistic lipid composition**, the simplest and most significant **interactions in terms of protein/lipid**, in order **to guide the docking experiments** and show the importance of the interaction of a protein with a lipid towards its structural and functional properties.

What is the role of lipids in the structure and the function of the μ receptor ?

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Methods

Generation of all-atoms model membranes
Membrane builder

↓

Simplifying with a coarse-grained model
Force field MARTINI
(+/- μ protein)

↓

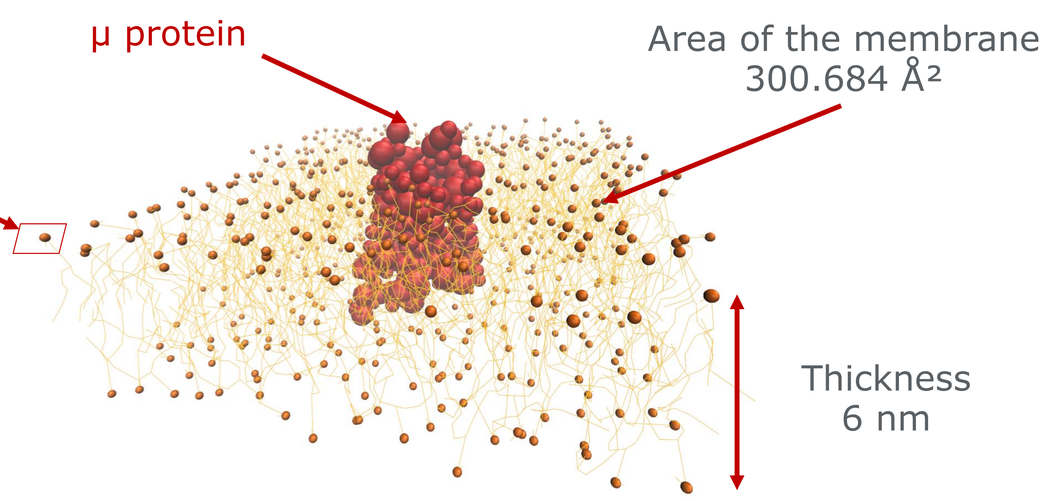
Molecular dynamics (NAMD 2.9)
500 ns (equilibration NVT, production NPT)

Results

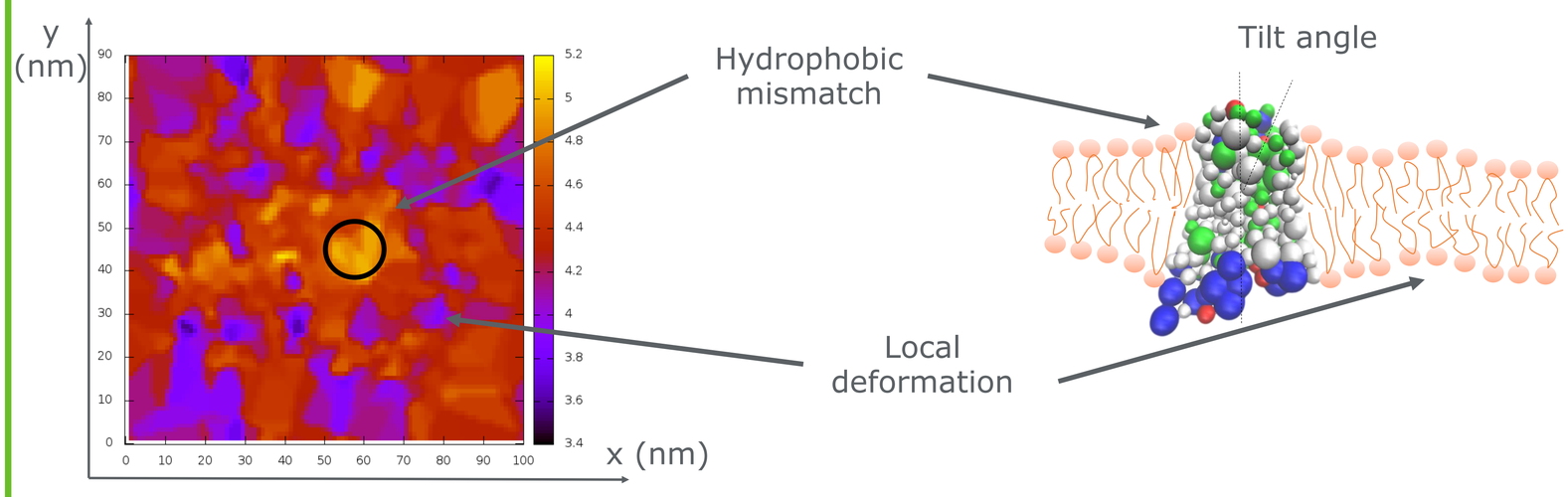
1- Controls

Area per lipid (Å²)

DPPC	63
POPC	68.3
POPE	63



2- Adaptation lipids/protein

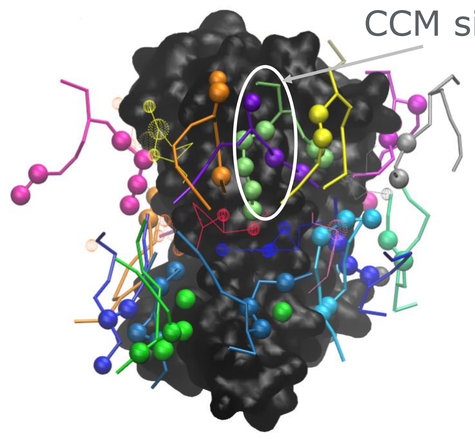


Visualization of the thickness with a color gradient (left).
Membrane of POPC and μ protein (black circle) in top view.
Adaptation of the protein in the membrane, tilt angle of 6° (right).

3- Interactions μ protein/lipids

Cholesterol Consensus Motif (CCM) characterized by 4 residues : W/Y (4.50), I/V/L (4.46), K/R (4.39-4.43) and F/Y (2.41).

Cholesterol can be replaced by the carbon chain of the POPC in the CCM site (conserved in the class A of GPCRs) which is the case here.



Annulus lipids
Lipids at 5 Å of the μ protein
POPC and cholesterol

Conclusion

The MD simulations have shown the adaptation of the membrane protein to the lipids by the relaxation around the protein and in return the inclination of the protein to minimize mismatches.

To understand the protein/lipid interactions, we looked specifically at the sites of interactions of lipids on the μ protein. Indeed, the crystal structure of the μ protein included a cholesterol [2]. GPCRs have binding sites cholesterol as CCM sites, found for μ protein also.

The nature of this interactions will be analyzed more precisely with all-atoms models. This will make it possible to understand the assembly of dimers guided by interactions between cholesterol of the *annulus* lipids.

References

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