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Analysis of the interaction of cannabinoids with their human CNR1 and CNR2 receptors

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INTRODUCTION

Cannabinoids are of growing economic interest with the rise of the medical and recreational cannabis industry. Cannabis-derived compounds, such as delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD), have demonstrated analgesic, anti-inflammatory, anxiolytic, and neuroprotective properties, offering promising prospects for the treatment of various conditions.¹ For example, oral cannabis extracts are effective against pain related to multiple sclerosis, chemotherapy-induced nausea and vomiting, and even certain forms of epilepsy. Consumers also use CBD recreationally to relieve stress or anxiety and promote a general sense of well-being, without the psychotropic effects associated with THC.¹

Additionally, CBD is frequently incorporated into products such as oils, capsules, gummies, and beverages, offering a variety of options for those seeking to benefit from its advantages. This dual interest, both medical and recreational, makes this topic a promising field with a rapidly growing industry, with great hopes in endometriosis for example. In 2020, more than 150 minor cannabinoids, collectively representing less than 1% of the total dry mass of cannabis flowers, were identified. These plant-derived molecules are classified in the family of phytocannabinoids, one of the three major families of cannabinoids, along with endocannabinoids and synthetic cannabinoids. Among human endocannabinoids, at least two have been identified: anandamide (AEA) and 2-arachidonoyl glycerol (2-AG). The main targets of these molecules are cannabinoid receptors 1 (CB1) and 2 (CB2), which are class A G protein-coupled receptors (GPCRs),² that are part of the analgesic reaction. Also, some studies suggest that phytocannabinoids can inhibit the Fatty Amino Acid hydrolase 1 (FAAH1) which decreases the endocannabinoids concentration in the organisms by breaking their peptide bonds. The inhibition can maintain a high level on endocannabinoids, prolonging the analgesic effect.³

The goal of this study is to understand the putative binding mode of endo- and phytocannabinoids into the two receptors CNB1 and 2, and study their impact on the dynamics behaviour of those systems. Molecular dynamics simulations and docking approaches have been used to answer those interrogations.

METHODS

Initial structures of the CNR1 and CNR2 available on PDB (PDB id: 5TGZ, 5ZTY)

- Completing the three existing structure by comparative modelling using Modeller⁴ and other tools to verify the quality.

- Protonation at pH 7 (H++⁵).

- Realistic membrane model for CB1 (neuron membrane) and CB2 (immune membrane).

- MD simulations have been realised on those systems using the CHARMM-36m⁶ force field in apo and holo forms using Gromacs⁷ with three replicates of 1 μ s each time.

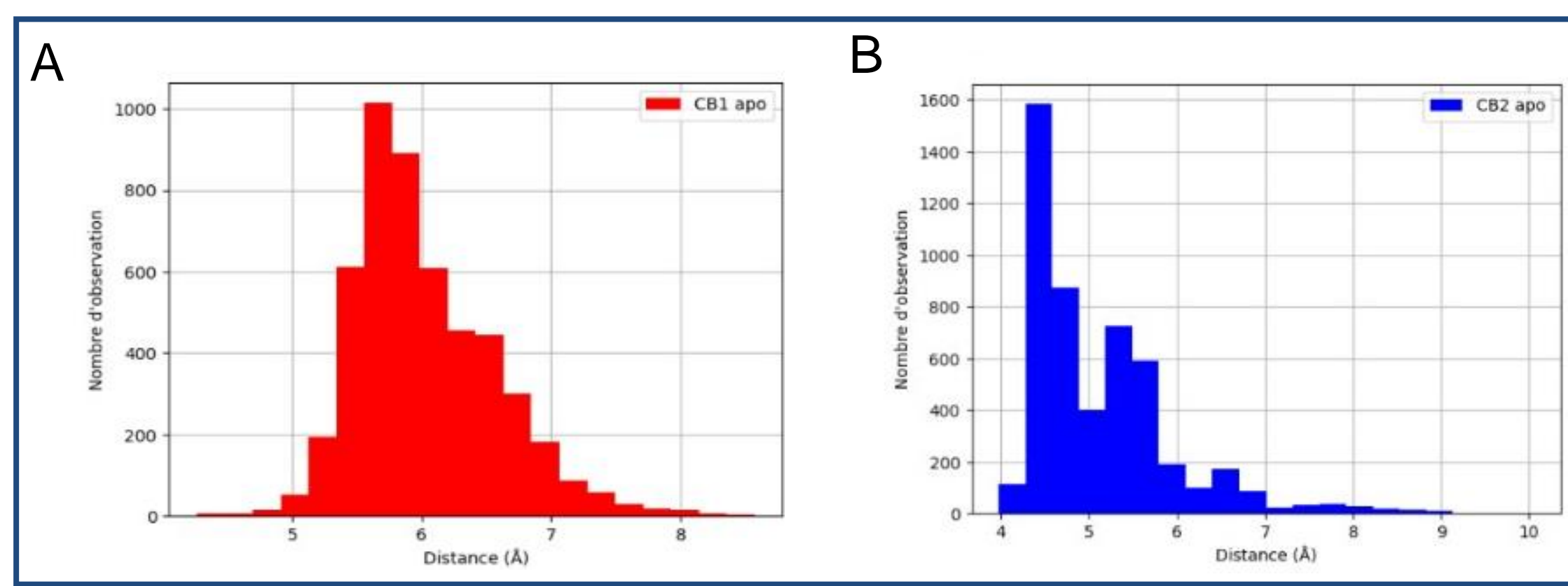
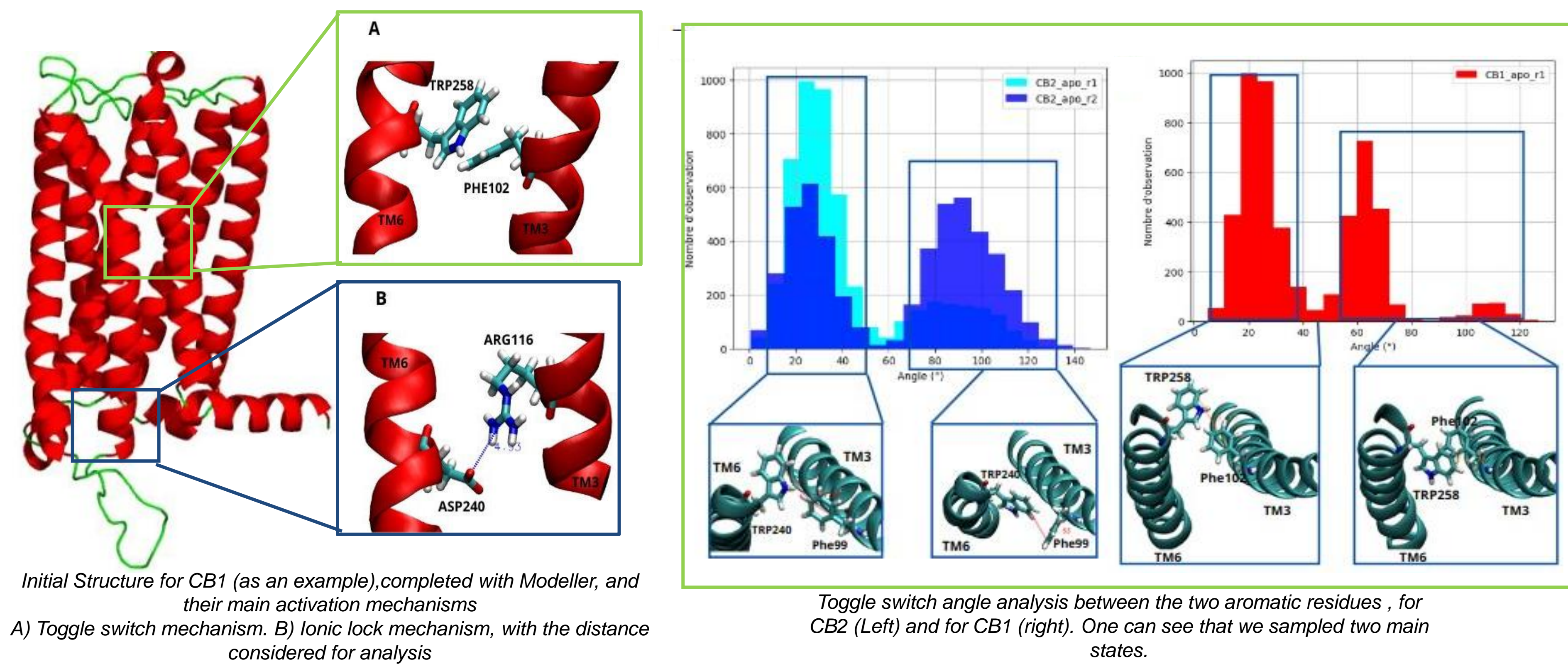
- 8 different systems, 14 μ s simulated in total.

Ligands Docking (CBD, THC, THC7 and H4CBD):

- AutoDock VINA 2021⁸

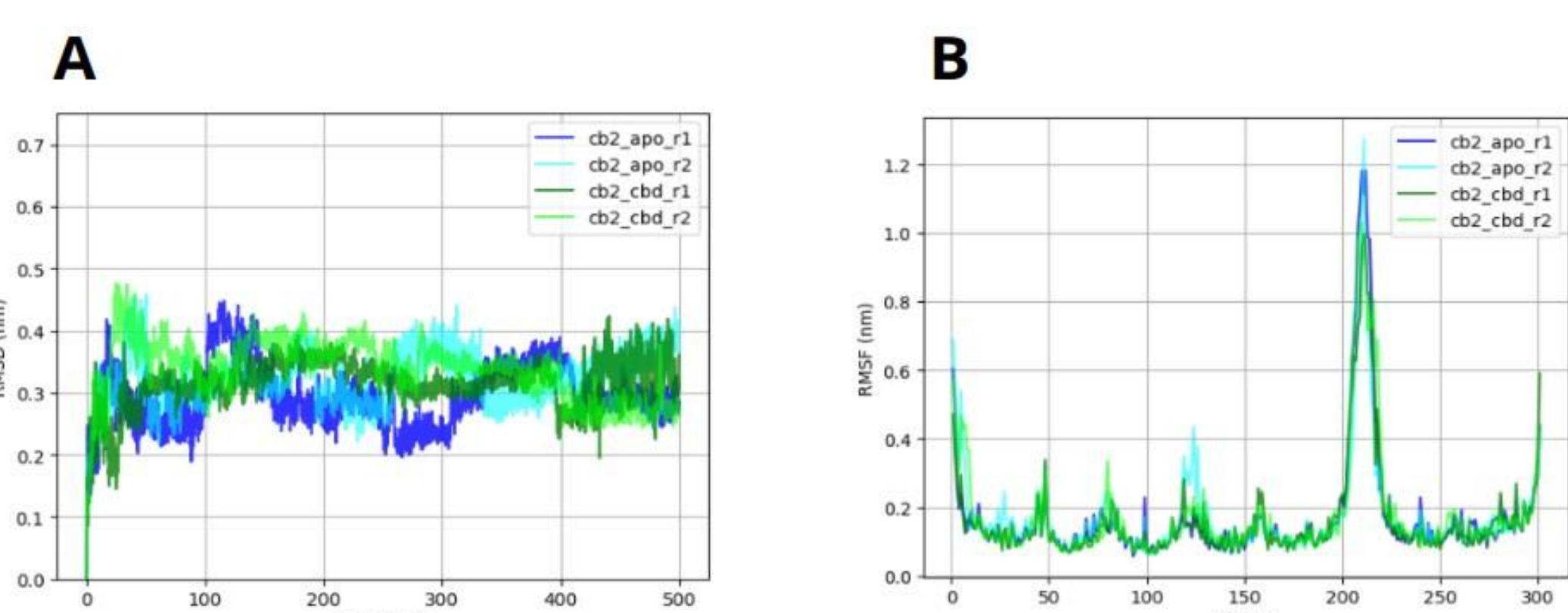
RESULTS

1) Sampling of apo proteins from molecular dynamics simulations



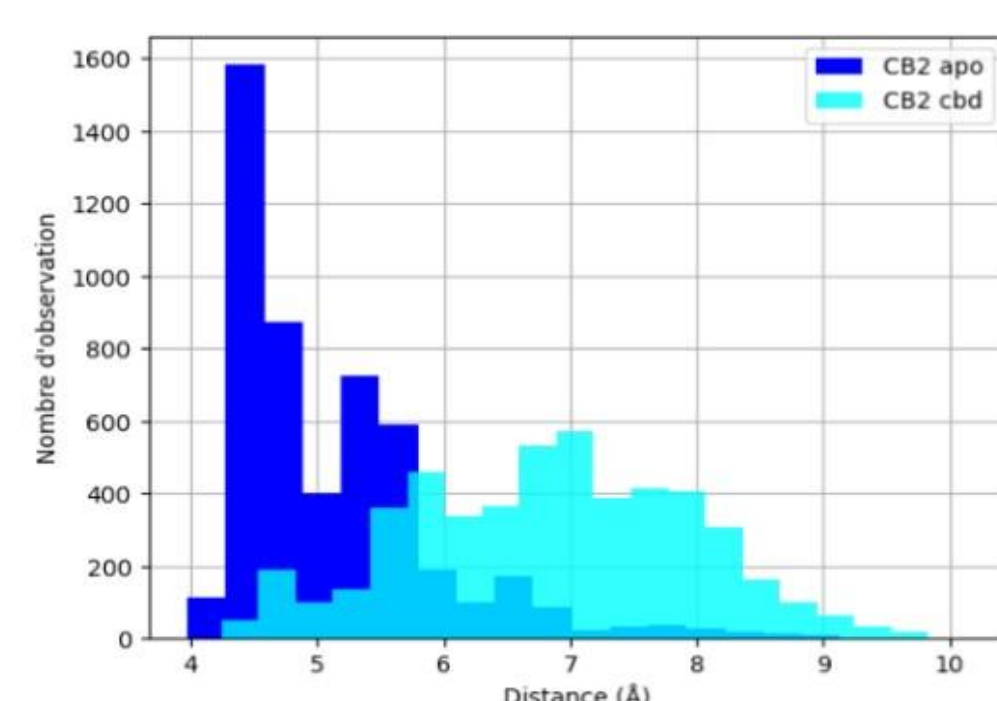
MD simulations of apo receptors reveals **large set of conformations sampled** including some in which **the ionic lock is opened and the toggle switch wide open**, that could lead to **receptors activation**

3) Simulation with ligand and their impact of the behaviour of CB1/2

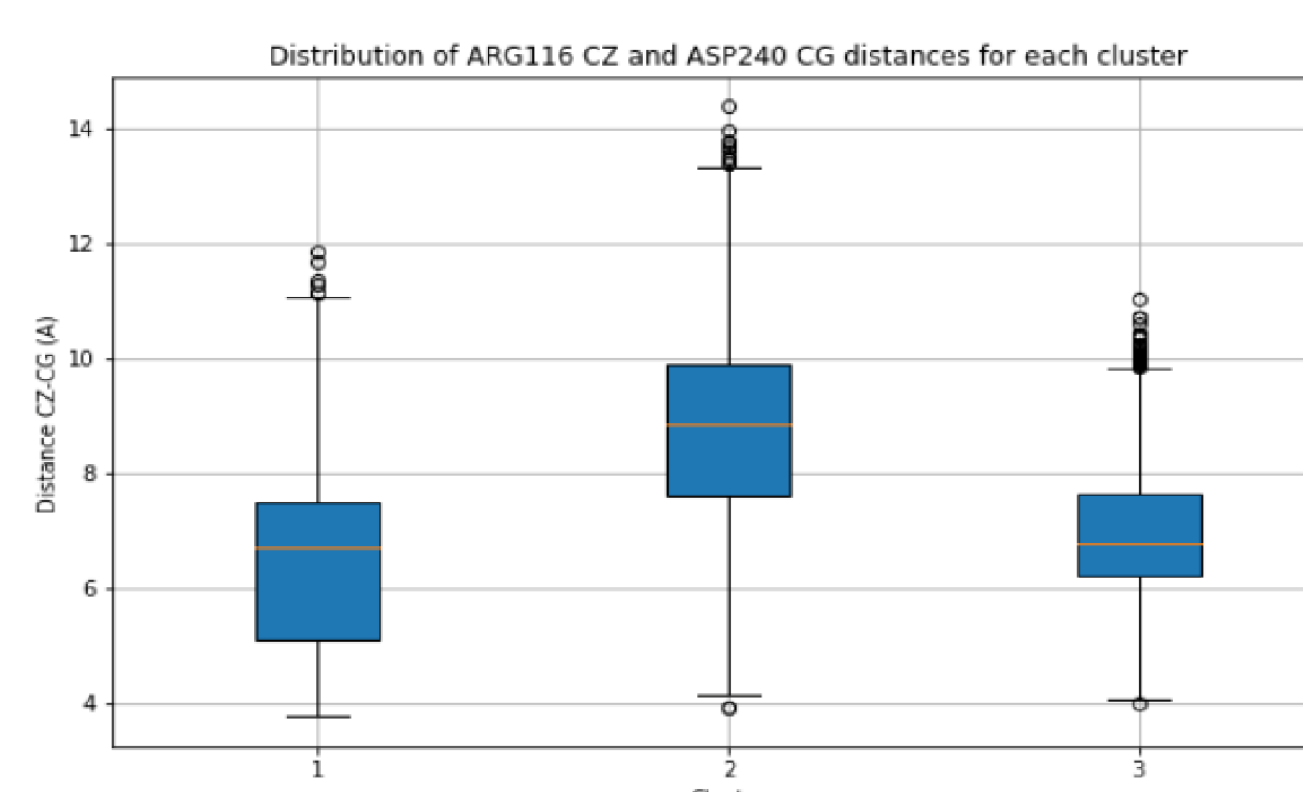
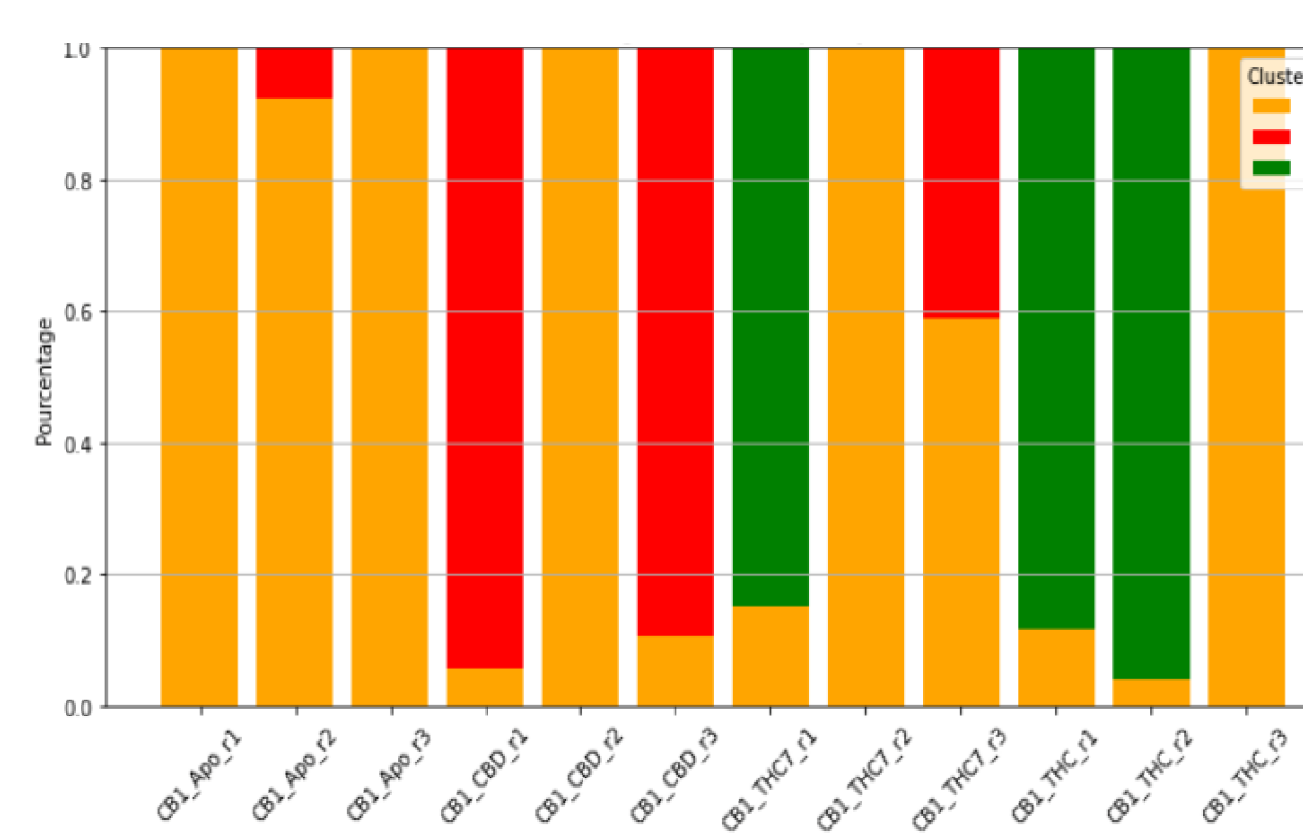


RMSD (A) and RMSF(B) comparison between apo CB2 and in complex with CBD compound.

Ionic lock distance distribution between CB2 apo system and CB2 in complex with CBD compound



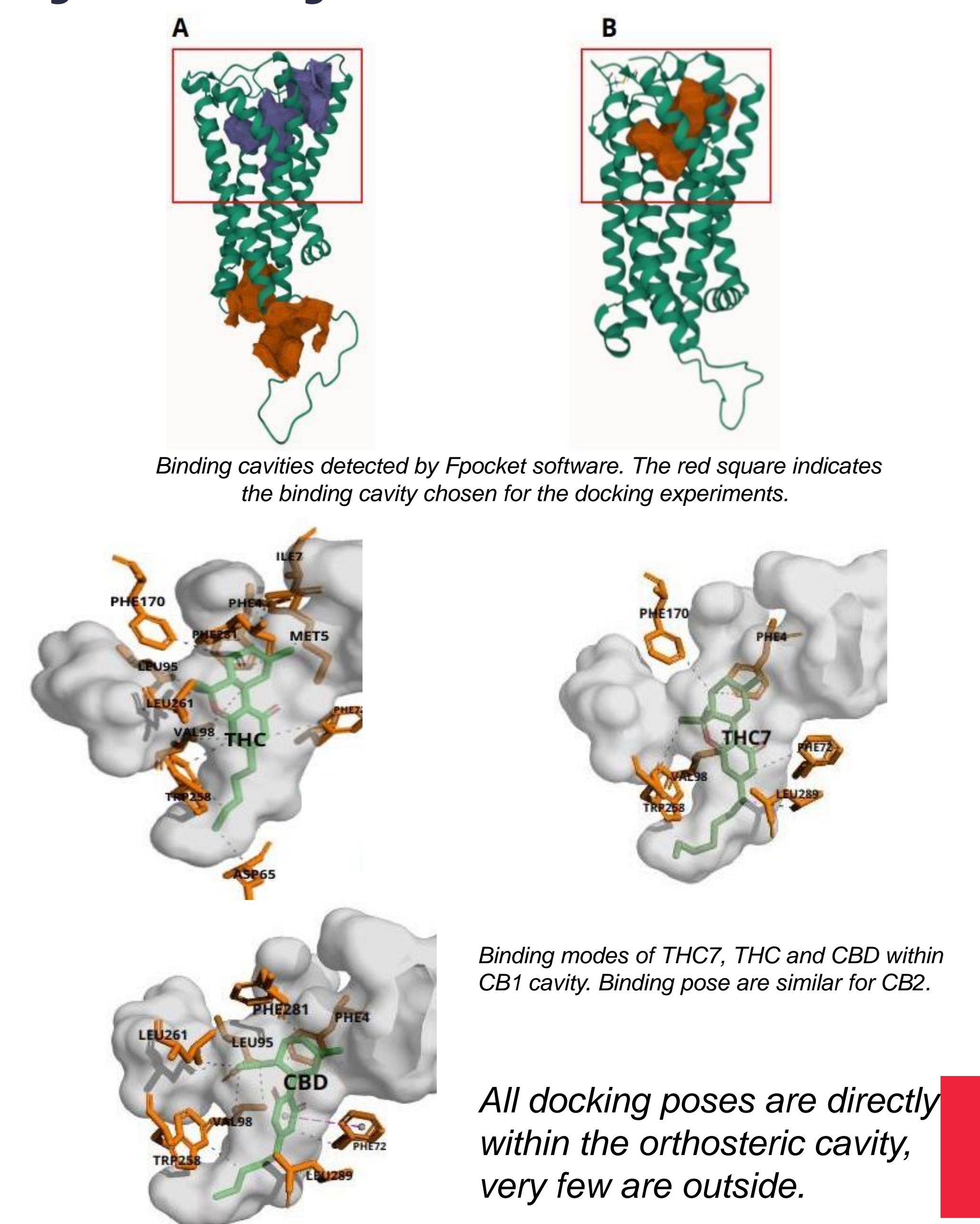
Evolution of ionic lock distances within the three clusters identified with hierarchical clustering



Globally, the binding of ligands seems not to impact the global dynamics of CB2. However, we can notice that the sampling is more spread regarding the ionic lock distance, with an increasing of the sampling of high distances

Hierarchical clustering of all CB1 MDs show three main clusters: It appears that CBD compound allow the sampling, in the case of CB1, mainly of the cluster N°2 in which the distance of the ionic lock is high. That could mean a switch to an active state

2) Ligands docking within CB1 and CB2



TAKE-HOME MESSAGES

- CB1 and CB2 can by themselves switch to some active-like conformations, such as we can expect for receptors with basal activity.

- The predicted binding modes of phytocannabinoids compounds within CB1 and 2 are very similar.

- For CB1 and 2, simulations with ligands does not truly change the dynamics behaviour of the receptor, however, we observe a larger sampling of conformations with high distance of ionic lock.

- Further calculations are required to fully understand ligands impact on those GPCRs.

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