Description of conformational landscape of a G protein-coupled receptor integrating Molecular Dynamics simulations with machine learning techniques

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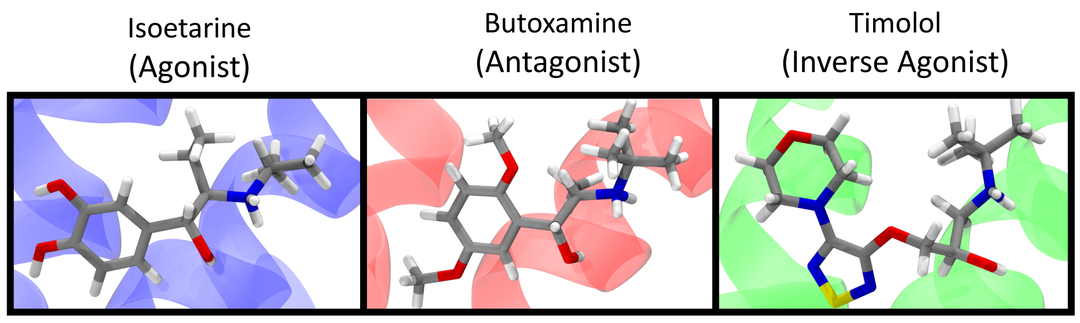
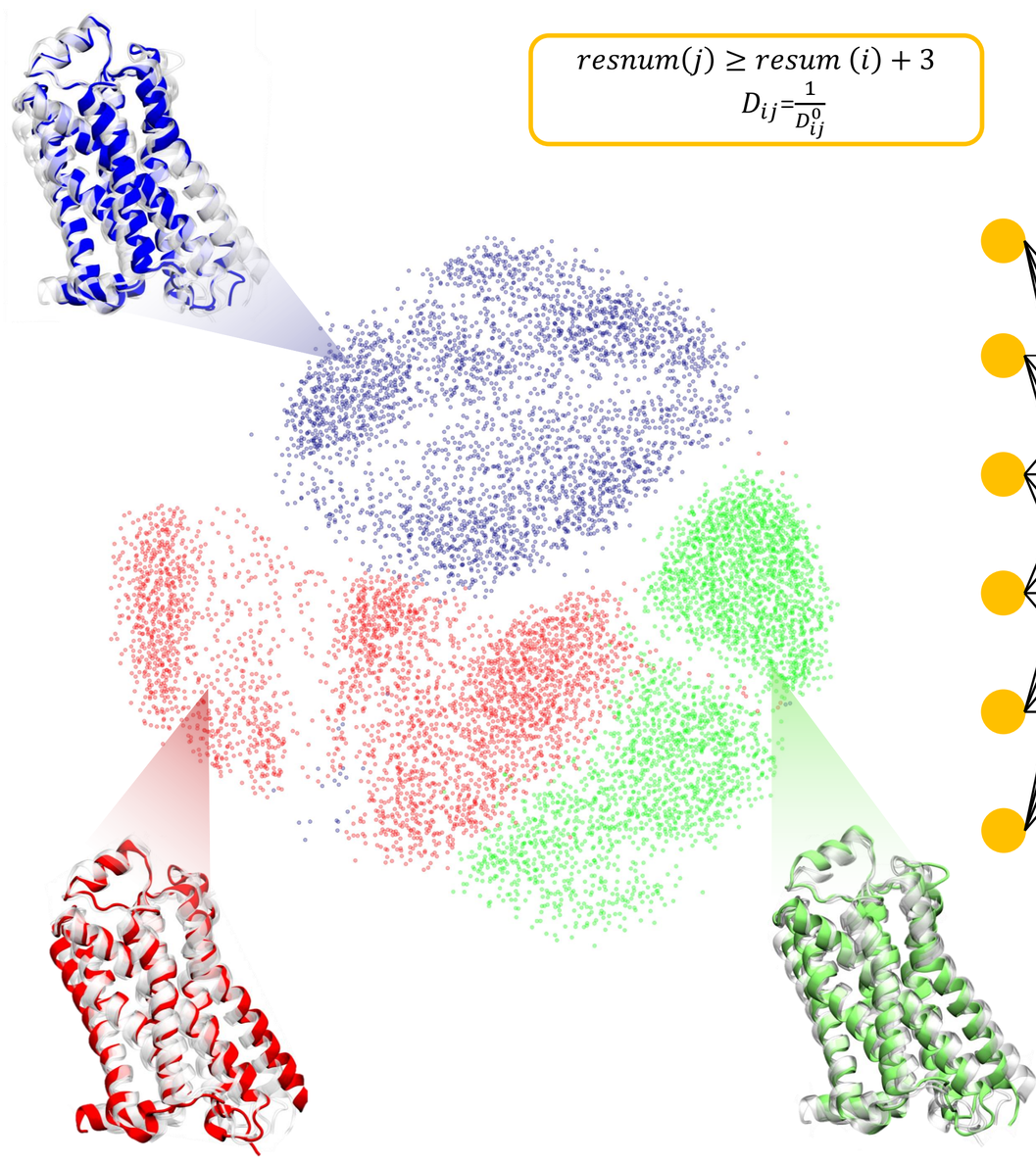
Introduction

- G-Protein coupled receptors are biomolecular targets of pharmaceutical relevance which undergo relevant structural changes upon ligand binding.
- Previous works focused on the β2-Adrenergic receptor as a case study to explore the integration of atomistic Molecular Dynamics simulations with machine learning techniques[1],[2] to characterize the receptor conformational changes.[3],[4],[5]





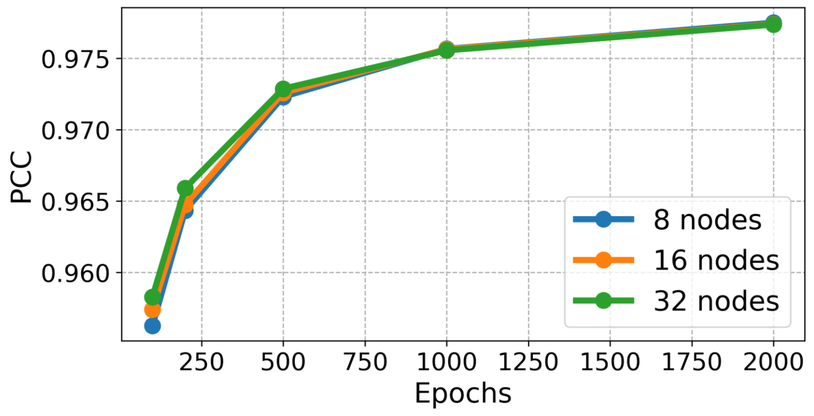
In these pictures, colors are related to the pharmacological profiles of ligands: points of unbiased trajectories with Isoetarine (Agonist) are in blue, with Butoxamine (Antagonist) in red, and with Timolol (Inverse Agonist) in green.

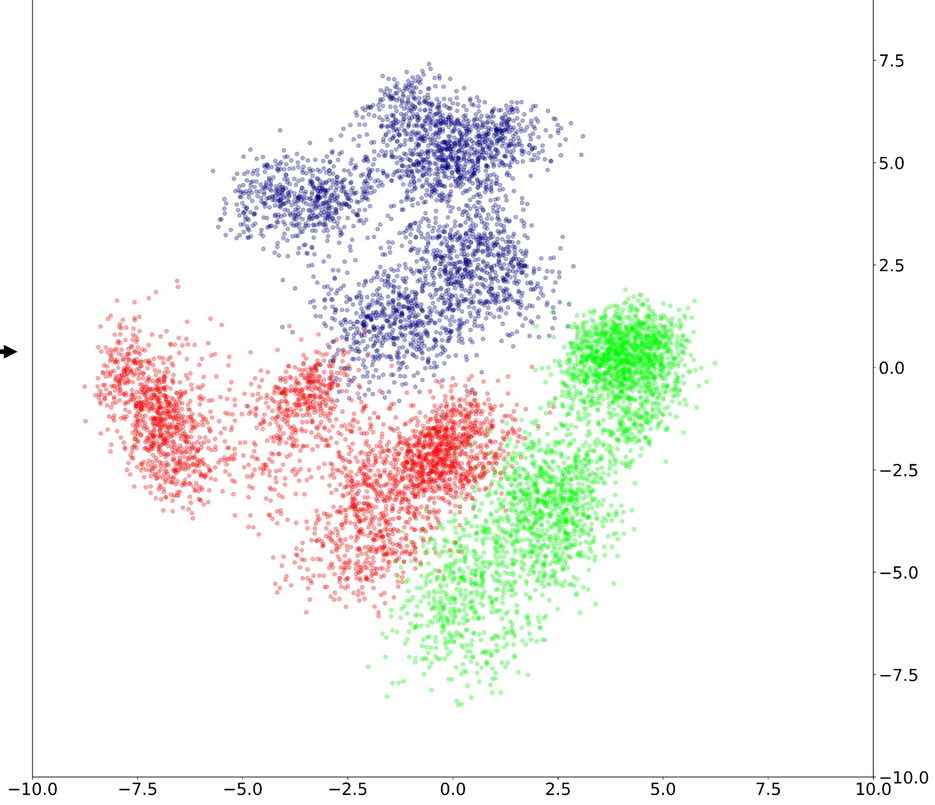
Methods

- Unbiased simulations:

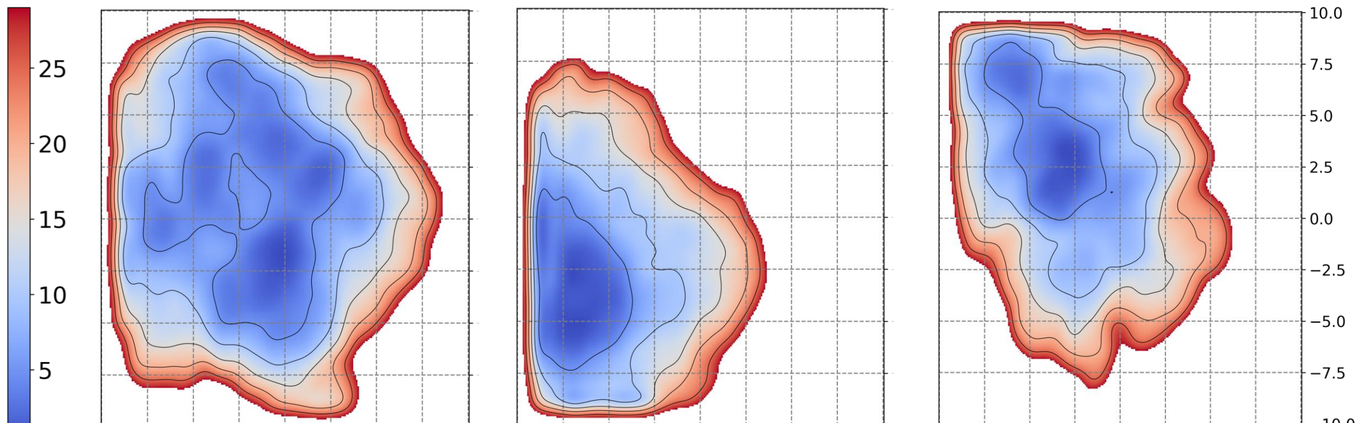
Ligand	Class	simulation t (ns)	# Replicates	total simulation t (ns)
Isoetarine	Agonist	500	3	1500
Butoxamine	Antagonist	500	3	1500
Timolol	Inverse Agonist	500	3	1500

- MDS (via Scikit-Learn) based on the Cα distances computed on the unbiased simulations.
- Biased simulations (via Plumed 2.7 – ANN module) using the Anncolvar package to approximate the MDS space through Neural Networks.[6]





Preliminary results



Well-Tempered Metadynamics:

- Hills height: 0.48 kcal/mol
- Hills width: 0.5
- Bias factor: 10
- Deposition time: 1 ps
- Simulation time: ≈ 150 ns

Perspectives

- In the course of this work, we aim at characterizing the effects of ligand binding on the free energy surface of β2-adrenergic receptor.
- In the long term, our procedure could be extended to explore the behaviour of the collective variables for the prediction of the pharmacological profile of ligands that were not considered in the training phase.

[1] Bernetti, M. *et al*. *Pharmaceuticals,* **2020**, *13*(9), 253
[2] Ceriotti, M. *Journal of Chemical Physics*, **2019**, 150(15), 150901
[3] Fleetwood, O. *et al*. *Biochemistry*, **2020**, 59(7), 880–91
[4] Fleetwood, O, *et al*. *Biophysical Journal,* **2020**, 118(3), 765–80
[5] Fleetwood, O. *et al*. eLife, **2021**, 10, e60715
[6] Trapl, D. *et al*.2019. Frontiers in Molecular Biosciences, **2019**, 6, 25

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