On the intrinsic flexibility of the μ opioid receptor through multiscale modeling approaches

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Abstract:

G protein-coupled receptors (GPCRs), one of the most important classes of therapeutic targets in the pharmaceutical industry, are very flexible proteins exhibiting a large spectrum of conformations depending on the type of ligand, the oligomerization state, etc [1]. Recent releases of numerous GPCR X-ray crystalline structures created the opportunity for computational methods to widely explore GPCR dynamics. Herein, we study the biological implication of the intrinsic flexibility properties of μ opioid receptor (μOR), a key protein in the medical field as the target of most used anesthetic agents. To do so, one first performed classical all-atom (AA) Molecular Dynamics (MD) simulations of μOR in its apo-form [2]. We highlighted that the various degrees of bendability of the α-helices present important consequences on the plasticity of the μOR binding site. Hence, this latter adopts a wide diversity of shape and volume, explaining why μOR can interact with diverse ligands presenting various structural 3D geometries. In the second part, one introduce a new strategy for parameterizing simple but precise coarse-grained (CG) elastic network models (ENMs) of μOR [3]. Optimized CG ENMs reproduced in a high accurate way the flexibility properties of μOR as observed during the AA MD simulations, proving that the helical bendability of GPCRs can be efficiently studied with purely mechanical CG models. Interestingly, our strategy is relevant at different CG resolutions [3], illustrating the hierarchical conservation of μOR flexibility properties. In the last part, ones uses network modularization techniques to design so-called multi-grained (MG) models [4]. They represent a novel type of low resolutions models, different in nature *versus* CG models as being true multi-resolution models, *i.e.*, each MG interaction site grouping a different number of residues. MG models, reproducing in a high accurate way the dynamics obtained with the AA MD simulations, are reliable for simulating the dynamics of μOR at a domain or modular resolution. In this way, the three parts of our work constitute altogether an integrated hierarchical and multiscale approach for understanding the intrinsic flexibility properties of μOR, starting from MD simulations, at computationally expensive but detailed AA scale, then used as reference to develop purely mechanical CG models of μOR, these latter being themselves spatially abstracted to design new and original MG models, highlighting modular features of μOR flexibility properties.

References:

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