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An active conformation of mGlu2 receptor induced by molecular dynamics simulation with C-terminal G_i peptide

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Recent progress in crystallization of the G Protein-Coupled Receptors opens new avenues for structure-based drug design approaches. Emergence of new crystal templates allows development of more precise models, and although already published research point out the importance of crystal structure resolution, quality and selection of proper template (or even using multiple ones)[1], homology modelling remains bread and butter of structure-based studies.

Homology modelling procedures are inherently connected with the problem of the presence of the template co-crystalized with the desired type of a ligand. Agonists, as they force active state of the receptor are significantly less represented in the available crystal structures, and the process of transforming homology model or even crystal structure into its activated conformation is a challenging task, involving use of either long term Molecular Dynamics simulations or homology modelling based upon more distant templates.

Here we present a novel method of inducing active conformations of GPCRs with the help of the C-terminal peptide of G protein as a cofactor restraining simulation system into desired active form. The case study of non-trivial target, Metabotropic Glutamate Receptor 2, being a class C GPCR, where the conformations received from simulation runs with and without G peptide probe, is evaluated in retrospective virtual screening procedure. The results show undoubtful advantage of the former approach, leading to relatively simple MD procedure and shorter simulation times and providing significantly better results in screening-like experiments.

[1] Rataj K., Witek J., Mordalski S. et al. *J. Chem. Inf. Model.* 54 (2014) 1661.

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