Role of structural flexibility for signal transduction by G protein coupled receptors

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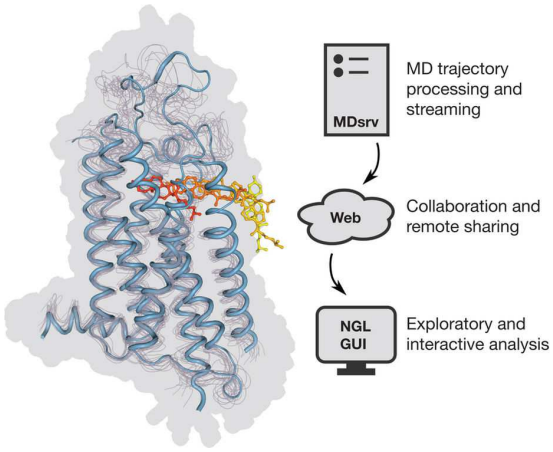

Flexibility is an essential structural feature of proteins transferring substances or information through membranes. G protein coupled receptors (GPCRs) are specialized 7-transmembrane helix bundle proteins which conduct a high variety of different extracellular signals into the cell through binding and activation of downstream signaling proteins such as heterotrimeric G proteins: Gi, Gs, Gq, G11/12 or arrestin 1-4. More than 800 different human GPCRs can couple to one or several downstream signaling partners, which raises the issue of coupling specificity, especially with regards to pharmacological intervention strategies targeting GPCRs which are major drug targets. Combination of existing structural biophysical data with data obtained from molecular dynamics simulations [1-3] suggest that structural flexibility of GPCRs does not only play a role for receptor activation but is also a key determinant for fast and specific signal transfer to G proteins. In light of increasingly interdisciplinary research and remote collaborations, it is desirable to make the atom trajectories of MD simulations widely available to facilitate interactive exploration and collaborative visual analysis as well as to promote discussions. For that purpose we developed MDsrv, a tool to stream MD trajectories and show them interactively within web browsers without requiring advanced knowledge in specialized MD software [4].

[1] Elgeti, M. *et al.* Precision vs flexibility in GPCR signaling. ***J. Am. Chem. Soc.***, 2013**, 135,** 12305–12.

[2] Rose, A. S. *et al.* Position of Transmembrane Helix 6 Determines Receptor G Protein Coupling Specificity**. *J. Am. Chem. Soc.***, 2014**, 136,** 11244–11247.

[3] Rose, A. S. *et al.* Role of Structural Dynamics at the Receptor G Protein Interface for Signal Transduction**. *PLoS One***, 2015, **10,** e0143399.

[4] Tiemann, JKS et al. MDsrv: viewing and sharing molecular dynamics simulations on the web. ***Nat. Methods***, 2017, 14, 1123-1124.