Revealing the selectivity determinants of ternary GPCR-complexes by homology modeling and molecular dynamics simulations

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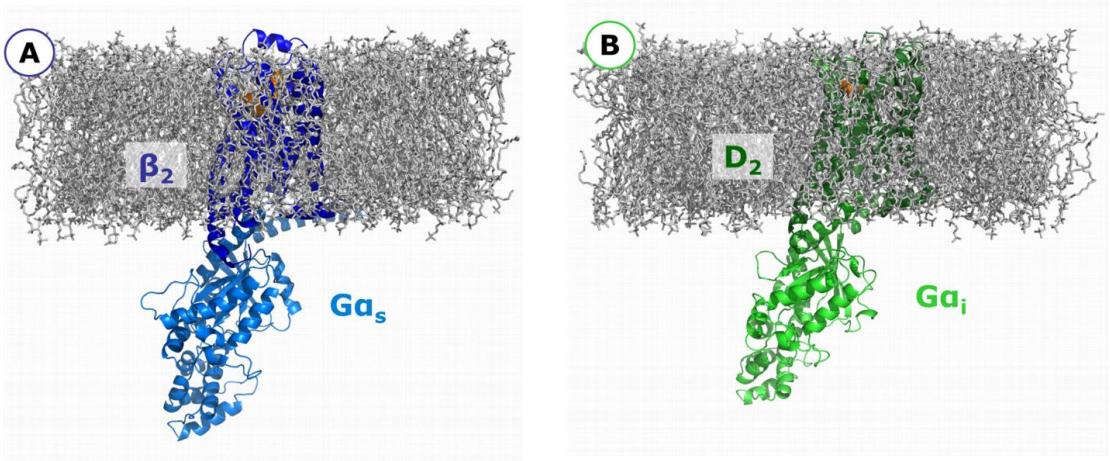
G protein-coupled receptors (GPCRs) are proteins that enable signal transduction through membranes by activating G proteins. Despite many investigations, the selectivity determinants of this interaction on the amino-acid level remain to be discovered.

A recent publication on the crystal structure of the β_2-adrenergic receptor in complex with its cognate G_s protein offers important structural insights into the nucleotide-free ternary signaling complex [1]. We use the β_2-Gα_s-structure (A) as a template to generate a homology model of the D_2-Gα_i complex (B). For both systems, β_2-Gα_s and D_2-Gα_i, long term all-atom molecular dynamics simulations in a hydrated lipid bilayer identify distinct amino-acid contact sites within the receptor-G-protein interface. Investigation of these interfaces by computational alanine scanning reveals amino-acid hot spot residues that presumably contribute to receptor-G-protein selectivity.



[1] S.G. Rasmussen, Nature 2011, 477, 549-555