Metadynamics-based protocols applied to G-protein Coupled Receptors

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G protein-coupled receptors (GPCRs), which represent the largest family of membrane proteins in the human genome, play important roles in signal transduction by detecting extracellular stimuli and activating intracellular downstream signaling pathways. Signaling by GPCRs usually occurs via ternary complexes formed under cooperative binding between the receptor, a ligand, and an intracellular binding partner (a G-protein or β-arrestin). The three processes associated with GPCR signaling are ligand binding/dissociation, which we have traditionally called ligand binding/unbinding, receptor activation/inactivation and G-protein coupling/uncoupling. These processes are usually very slow in comparison to typical molecular dynamics (MD) simulation times (several μs to a millisecond), so that either enhanced sampling or steered MD techniques are needed to investigate them. Metadynamics has proven to be very successful for reconstructing the free energy hypersurface and for accelerating rare events in complex biomolecular systems. However, metadynamics is limited in the number of collective variables (CVs) it can handle as the computational cost scales exponentially with the number of CVs, hence finding and improving CVs is the object of intense investigation. Our own work in this field includes developing metadynamics protocols to investigate different steps in the GPCR signaling process. For receptor activation, we defined a generally applicable activity index[1] (A^{100}) for class A GPCRs. This index is a linear combination of five inter-helix distances between α-carbons that allows us to characterize the activation state. This activity index represents an effective CV for simulating activation/deactivation free-energy profiles for class A GPCRs with metadynamics.[2] A further important development is that our binding/unbinding protocol for small-molecule ligands[3] has been adapted and extended to consider peptide ligands for class A GPCRs.[4] This extension requires that the conformational sampling, the mechanical integrity, and the extension into the extracellular medium of the protocol be improved. These new metadynamics-based protocols generate results compatible with previous simulation and experimental studies at a relatively low computational cost.

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