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Predicting Cholesterol Interaction Sites on GPCRs using Coarse-Grained MD RICK SEXTON, Arizona State University, Department of Physics, JAMES GEIGER, ZINA AL-SAHOURI, EUGENE CHUN, MING-YUE LEE, WEI LIU, Arizona State University, Biodesign Institute, Center for Applied Structural Discovery, OLIVER BECKSTEIN, Arizona State University, Department of Physics and Center for Biological Physics — Cholesterol has been shown to be important to the function of G-protein coupled receptors (GPCRs), the largest class of signaling membrane proteins and the largest class of drug targets in the human genome. However, experiments cannot always reveal how a specific GPCR and cholesterol molecule interact. We developed a method based on molecular dynamics (MD) simulations to predict sites on the protein where the cholesterol may interact. A limitation of all-atom MD is the computational cost to sample even a few s of simulation time. In order to sample longer time scales (tens of s), coarse-grained MD simulations were preformed and analyzed for several GPCRs, including the beta-2 adrenergic receptor and the cannabinoid receptors CB1 and CB2. The computed off rates (k_{off}) or equivalently, the average waiting time in the bound state, show a difference in cholesterol binding for CB1R and CB2R, where CB1R has been shown to bind to cholesterol and CB2R does not. For the proteins in which cholesterol binds, we identified several residues of interest that agree with electron densities from crystallographic measurements and known cholesterol binding motifs. In summary, we developed a physics-based method to predict cholesterol binding sites in GPCRs (and potentially other membrane proteins) and validated it using experimental data.

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