sliceGPCR: Predicting Biased Signaling in Drug Targets Using Novel Volumetric Protein Imaging and 3D Convolutional Neural Networks

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G protein-coupled receptors (GPCRs) are one of the most therapeutically important receptor families, being the target of >30% of FDA-approved drugs. Activating a GPCR changes its shape, allowing it to activate 2 pathways: G-protein and ß-arrestin. Biased signaling, where a drug shapes the receptor to selectively activate one pathway over the other, is a promising strategy for developing therapeutics with minimal side effects. However, the structural mechanisms driving pathway selectivity remain poorly understood. Using a novel structural imaging technique, my project developed a deep-learning model to classify G-protein- and ß-arrestin-biased receptors by analyzing their shapes. I developed a computational approach where I "slice" GPCR structures along the z-axis to generate cross-section images, like MRI scanning. For each image, I produced three channels capturing surface geometry, helical architecture, and aromatic sidechains, used as inputs for a 3D convolutional neural network (CNN). To validate my slicing methodology, I trained a CNN on 400 active and inactive GPCR structures, achieving 95% accuracy in distinguishing active from inactive conformations, confirming that z-axis slices capture meaningful structural differences. I then trained another CNN on nearly 800 GPCRs in G-protein- versus ß-arrestin-bound conformations, achieving 99% classification accuracy. This model predicted every experimentally confirmed biased receptor correctly. I also identified which slices most influenced predictions, providing interpretable insight into the structural features driving pathway selectivity. These results demonstrate that GPCR slicing combined with 3D-CNNs can decode biased signaling, offering a novel tool for structure-based drug discovery.

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