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Modeling G protein-coupled receptors in human genome

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Abstract:
G protein-coupled receptors (or GPCRs) are integral transmembrane proteins responsible to various cellular signal transductions. Human GPCR proteins are encoded by 5% of human genes but account for the targets of 40% of FDA approved drugs. Due to the difficulties in crystallization, experimental structure determination remains difficult for human GPCRs, which have been a major barrier in modern structure-based drug discovery. We proposed a new hybrid protocol, GPCR-I-TASSER, to construct GPCR structure models by integrating experimental mutagenesis data with ab initio transmembrane-helix assembly simulations, assisted by the predicted transmembrane-helix interaction networks. The method was tested in recent community-wide GPCRDock experiments and constructed models with a root mean square deviation 1.26 Å for Dopamine-3 and 2.08 Å for Chemokine-4 receptors in the transmembrane domain regions, which were significantly closer to the native than the best templates available in the PDB. GPCR-I-TASSER has been applied to model all 1,026 putative GPCRs in the human genome, where 923 are found to have correct folds based on the confidence score analysis and mutagenesis data comparison. The successfully modeled GPCRs contain many pharmaceutically important families that do not have previously solved structures, including Trace amine, Prostanoids, Releasing hormones, Melanocortins, Vasopressin and Neuropeptide Y receptors. All the human GPCR models have been made publicly available through the GPCR-HGmod database at http://zhanglab.ccmb.med.umich.edu/GPCR-HGmod/ The results demonstrate new progress on genome-wide structure modeling of transmembrane proteins which should bring broad impacts on the GPCR-targeted drug discovery.

Biography:
Dr. Yang Zhang is a professor in the Department of Computational Medicine and Bioinformatics and the Department of Biological Chemistry, University of Michigan. The research interest of Dr. Zhang's Lab is in protein structure prediction and protein design. The I-TASSER algorithm developed in his lab was ranked as the No 1 method for automated protein structure prediction in the worldwide CASP competitions in 2006, 2008, 2010, 2012, 2014 and 2016. Most recently, his lab developed a new pipeline (GPCR-I-TASSER) for G protein-coupled receptors modeling and completed structure modeling and ligand-screening for all putative GPCRs in the human genome, where more than 80% were shown to have correct fold. Dr. Zhang is the recipient of the US National Science Foundation (NSF) Career Award in 2008, the Alfred P Sloan Award in 2008, and the Dean's Basic Science Research Award in 2013.