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Conformational entropic maps of functional coupling domains in GPCR activation: A case study with beta2 adrenergic receptor[1] FAN LIU, RAVINDER ABROL, WILLIAM GODDARD III, DENNIS DOUGHERTY, Cal Inst of Tech (Caltech) — Entropic effect in GPCR activation is poorly understood. Based on the recent solved structures, researchers in the GPCR structural biology field have proposed several "local activating switches" that consisted of a few number of conserved residues, but have long ignored the collective dynamical effect (conformational entropy) of a domain comprised of an ensemble of residues. A new paradigm has been proposed recently that a GPCR can be viewed as a composition of several functional coupling domains, each of which undergoes order-to-disorder or disorder-to-order transitions upon activation. Here we identified and studied these functional coupling domains by comparing the local entropy changes of each residue between the inactive and active states of the $\beta 2$ adrenergic receptor from computational simulation. We found that agonist and G-protein binding increases the heterogeneity of the entropy distribution in the receptor. This new activation paradigm and computational entropy analysis scheme provides novel ways to design functionally modified mutant and identify new allosteric sites for GPCRs.

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