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Automated fitting of allosteric parameters in receptor oligomer models

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Automated fitting of allosteric parameters in receptor oligomer models

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G protein-coupled receptors (GPCRs) are promising targets of neuropsychiatric drugs. GPCRs often function as oligomeric (multi-molecule) signaling complexes, e.g., metabotropic glutamate receptors are obligate dimers. Quantitative pharmacologists construct Markov chain models to give insight into the relationship between ligand concentration and the fraction of cell surface receptors in each of several molecular conformations. The molecular states and transitions of these receptor occupancy models explain gradations of cellular response. In prior work we have shown how allosteric interactions within receptor dimers can be enumerated by constructing a distinguished spanning tree of the Cartesian product of graphs (state transition diagrams) representing the states and transitions of each monomer [Smith and Hammack 2017 *ARS Math. Contemp.* 12:1, 2017]. Associated to this spanning tree is a rational polynomial encoding the probability of each molecular state as a function of ligand concentration (the ligand binding curve). Cell response is usually assumed to be a linear function of these probabilities [Conradi Smith *Math. Med. Biol.* 37:3, 2020]. Using this framework, we explore how allosteric parameters can be chosen to fit experimental observations of cell response dominated by receptors in the monomeric or oligomeric form, respectively. An information criterion is used to infer parsimonious subsets of allosteric interactions that are most likely responsible for observed differences between monomeric and oligomeric responses.