Receptor Allostery and Cycle Kinetics

Greg Conradi Smith | Product graphs and quantitative pharmacology
https://gregconradismith.github.io/

My research develops mathematical and biophysical models of receptor complexes, asking how ligand binding, conformational changes and interactions among protein subunits determine cellular signalling. I combine graph theory, continuous-time Markov chains and symbolic computation to connect molecular hypotheses with measurable binding and signalling responses. A central goal is to distinguish the consequences of receptor architecture and thermodynamic constraints from effects that require biochemical energy consumption.

Equilibrium allostery and product graphs

In collaboration with Richard Hammack (Virginia Commonwealth University), I developed a construction of cycle bases for reduced powers of graphs. These graphs describe collections of identical, indistinguishable subunits that need not behave independently. The cycle structure identifies the constraints required for microscopic reversibility, providing a systematic foundation for physically consistent models of receptor dimers and larger oligomers.[1]

My subsequent work uses distinguished spanning trees to express equilibrium oligomer occupancies and binding curves in terms of monomer properties and emergent allosteric parameters. The approach accommodates arbitrary monomer state graphs and does not assume independent subunits. Ternary-complex and cubic-ternary-complex GPCR models provide examples connecting ligand binding, G-protein association and receptor activation.[2] Current efforts address how much coupling information can be recovered from experimental observables, how to select parsimonious interaction models, and how uncertainty in monomer parameters affects inference for oligomers.

Nonequilibrium signalling and cycle kinetics

I am extending this framework to nonequilibrium receptor kinetics, where nucleotide exchange and hydrolysis sustain circulating probability currents. Current models separate receptor dynamics with fixed free-species concentrations from mass-action systems with finite receptor and G-protein pools. This distinction makes conservation laws, chemical driving and the meaning of measured turnover explicit. Tree-theorem calculations, cycle decompositions, deterministic simulation and stochastic simulation provide complementary checks on the resulting models.

An important question is which combinations of occupancy, turnover and transition-time measurements can identify underlying rates. Another is how conformational coupling changes signalling flux without introducing thermodynamically inconsistent driving. These mechanistic studies use illustrative parameter sets. To make the methods accessible, I am developing computational resources in SageMath and Python; the Receptor Modeling Jupyter Book provides worked examples of equilibrium and steady-state receptor analysis.[3] The goal is a reusable framework for interpreting receptor experiments and testing pharmacological hypotheses.

Selected publications and computational resource

1. Hammack RH, Smith GD (2017). Cycle bases of reduced powers of graphs. Ars Mathematica Contemporanea 12(1):183–203. doi:10.26493/1855-3974.856.4d2.

2. Conradi Smith GD (2020). Allostery in oligomeric receptor models. Mathematical Medicine and Biology 37(3):313–333. doi:10.1093/imammb/dqz016.

3. Conradi Smith GD (2025). Receptor Modeling Jupyter Book. Unrefereed computational resource supported by NSF DMS-1951646. gregconradismith.github.io/receptor-modeling-jupyter-book/intro.html

Funding: National Science Foundation DMS-1951646, Cycle representations of receptor complex signal transduction (Conradi Smith). Foundational cycle-basis work was supported by NSF DMS-1121606.