Abstract Submitted
for the MAR07 Meeting of
The American Physical Society

Interaction of Receptors and GTPase-Activating Proteins in a G Protein Signaling Module[1] MARC TURCOTTE, WEI TANG, ELLIOTT M. ROSS, University of Texas Southwestern Medical Center — We have developed a model of the interactions of proteins involved in G protein signaling using steady-state data from reconstituted vesicles. The model includes receptor, G protein (G), GTPase activating protein (GAP), GTP and GDP. Implementation is done using coupled ordinary differential equations. We performed a global fit to the model parameters against enzymologic and nucleotide-binding data using simulated annealing constrained by thermodynamics. Validation was done using Monte Carlo data. Fit parameters uncertainties were obtained via multiple repeats of stochastic searches. We studied fit parameter correlations near a solution by local thermal sampling of the cost manifold. The best fit parameters agree with values derived from dynamic data not used in our fit. We used our model to study signaling in familiar regimes and to predict new, testable behaviors in others. Signal output is a complex function of the inputs: receptor and GAP at physiologic and experimental concentrations of GTP and GDP. We studied the shape of the activation surface. Its complexity derives from stoichiometric relationships among protein concentrations. Our model predicts signaling pathways and dynamical response in G protein modules.

[1]NIH RO1GM30359, NIH K25GM071957, Welch Foundation I-0982

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Date submitted: 17 Nov 2006 Electronic form version 1.4