**Energy-based modeling reveals mechanisms of transient behavior in the EGFR pathway**

**Abstract**

Rule-based modeling is motivated by modular domain structure and combinatorial complexity of macromolecules. In rule-based modeling languages, such as BioNetGen, macromolecules are characterized using structured objects that correspond to the domain structure of their biological counterparts, and their transformations are governed by reaction rules. Although rule-based modeling approach offers a framework for representing multiple reactions with a single reaction rule, multiple rules are required to describe cooperative interactions. Here, using an energy-based extension to BioNetGen, we address the problem of regulatory complexity brought on by the cooperative interactions between different sites in the Epidermal Growth Factor Receptor (EGFR) signaling pathway. Although a vast number of both experimental and computational studies focus on EGFR signaling, the mechanisms underlying many features of the kinetics of EGFR signaling remain unknown. In this study, we use a systematic approach to explore the behavior of the EGFR pathway. We first develop an energy-based model of the EGFR signaling pathway using the BioNetGen language, which contains a number of cytoplasmic target proteins and leads to multiple cooperative interactions. The presented model is fitted to published experimental data demonstrating transient tyrosine phosphorylation of EGFR using parameter estimation approaches. [ONE OR TWO SENTENCES DESCRIBING THE FINDINGS] In addition, we performed sensitivity analysis to gain a deeper understanding of how cooperative energy parameters influence the transient generation. [BRIEF DESCRIPTION OF RESULTS]