**Energy 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 respond to the domain structure of their biological counterparts, and their transformation is governed by reaction rules. Despite the fact that rule-based modeling approach offers a framework for representing multiple reactions with a single reactions rule, it may face new challenges due to the 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 Epidermal Growth Factor Receptor (EGFR) signaling pathway. Although a vast majority of both experimental and computational studies focus on EGFR signaling, the kinetics and control mechanisms underlying the short term pattern of cellular responses in EGFR pathway remain unknown. In this study, we aim to use more systematic approaches 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 the experimental data demonstrating transient tyrosine phosphorylation of EGFR using parameter estimation approaches. On the other hand, a sensitivity analysis helps to gain a deeper understanding of how cooperative energy parameters influence the transient generation. It seeks to determine the mechanism(s) by which transients may arise in this system.