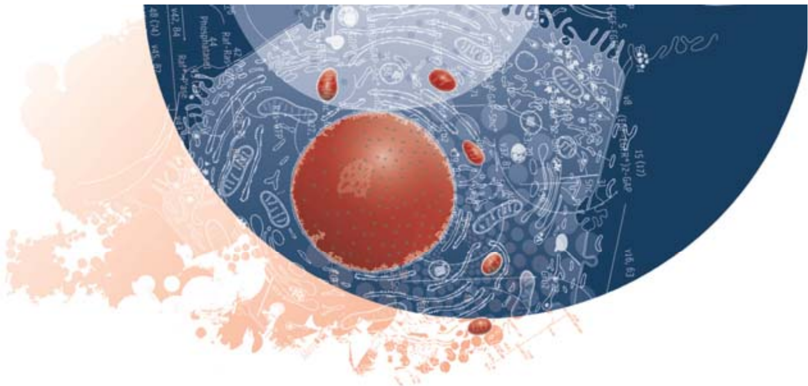
SBMC 2010 Conference on Systems Biology of Mammalian Cells
June 3rd-5th 2010 · Freiburg | Germany · Konzerthaus · www.sbmc2010.de



DYNAMIC REGULATION OF GROWTH FACTOR RECEPTOR SIGNALING NETWORKS

Jason Haugh

Department of Chemical and Biomolecular Engineering
North Carolina State University, USA

The concept of a signaling pathway provides a useful framework for understanding the flow of information as an ordered series of activation processes, exemplified by the Ras → Raf → MEK → ERK pathway and other mitogen-activated protein kinase (MAPK) cascades, which control diverse responses in cells stimulated by various growth factors and cytokines. Our current understanding of signal transduction, however, encompasses the concept of signaling networks, in which the canonical pathways interact with and thus affect one another (crosstalk); the sequential pathway concept is further challenged by the regulation of signaling through negative feedback and, in some cases, reinforcement of signaling through positive feedback. Although the concept of an integrated signaling network replete with inter-pathway crosstalk and feedback regulation is broadly appreciated, and kinetic models of signal transduction processes have steadily appeared over the past decade, it is fair to say that a more comprehensive data acquisition effort is needed to better constrain models at the network scale of complexity.

We demonstrate that models of signaling networks, trained on a sufficient diversity of quantitative measurements, can be reasonably comprehensive, accurate, and predictive in the dynamical sense. Our recent data-driven modeling efforts have quantified 1) the contributions of canonical (Ras-dependent) and crosstalk (phosphoinositide 3-kinase-dependent) pathways in the ERK signaling network [Wang et al. Mol Syst Biol, 5: 246 (2009)] and 2) their regulation by distinct negative feedback loops. The context of those measurements and models is platelet-derived growth factor (PDGF) stimulation of mouse fibroblasts, for which we have an extensive data repository. If time permits, a comparative analysis of the PDGF and fibroblast growth factor (FGF) receptor signaling networks will also be presented.