

Systematic Analysis of Crosstalk in Intracellular Signal Transduction Networks

Biomathematics Seminar

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An ongoing challenge in mammalian cell biology is to bridge the gaps in our understanding of processes at the molecular, cellular, and tissue levels. Central to the hierarchy of biological complexity is the field of *signal transduction*, which deals with the biochemical mechanisms and pathways by which cells respond to external stimuli, such as soluble growth factors/cytokines, immobilized ligands such as those found in extracellular matrix or the surfaces of other cells, and mechanical forces. Intracellular signaling processes control the growth, survival, and migration of cells in normal physiological contexts, and defects in signaling form the molecular basis for cancer, immune system disorders, and other diseases. Using a quantitative approach that combines biochemical measurements, live-cell fluorescence microscopy, and mathematical modeling, we seek to characterize signal transduction networks through analysis of their kinetics and spatial patterns in cells.

As an example of this approach, I will present our ongoing efforts to characterize signal transduction mediated by cell surface receptors for platelet-derived growth factor (PDGF), a soluble factor that accelerates dermal wound healing by directing the migration and proliferation of fibroblasts. The crux of the talk will detail our systematic elucidation and kinetic analysis of the so-called *crosstalk* interactions between two canonical signaling pathways that are strongly activated by PDGF receptors: the phosphoinositide 3-kinase (PI3K) and Ras/extracellular signal regulated kinase (Erk) pathways. A model of the network, formulated at an appropriate level of granularity, has enabled us to evaluate the contributions of PI3K-dependent crosstalk and Ras as quantifiable inputs that are integrated by Erk. We see this as an important step towards predictive modeling at the level of signal transduction networks.