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## Mathematical Models in Signaling Systems - June 16-18, 2004

### ***Analysis of Network Architecture***

#### *Analysis of Regulatory Loci within Signaling Networks*

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#### ***Abstract:***

Many intracellular signaling pathways interact with one another to form networks. These networks regulate cellular machines to evoke physiological responses. One such cellular function is the long-term potentiation of synaptic responses in hippocampal neuronal cells. Many signaling pathways are implicated in long-term potentiation. To understand how information flow is regulated and propagated within the cell we developed and analyzed a cellular regulatory network. For this we gathered information on the known pathways and the connections between them to construct a meso-scale network. The network representation follows the rules developed by Science's Signal Transduction Knowledge Environment (STKE) where nodes represent cellular components such as proteins, complexes of proteins or small molecules and interactions between nodes are represented by links that specify activation, inhibition or neutral interactions. The network contains around 500 components and 1100 interactions obtained from literature. Interactions include reversible non-covalent binding reactions, phosphorylation/dephosphorylation reactions, proteolytic reactions and other enzymatic reactions such as synthesis and degradation of second messengers. The fully connected network follows the small-world regime and contains several regulatory motifs that are more prevalent compared to motifs found in shuffled networks with the same connectivity. Characterizing these motifs we found that there is an abundance of circular motifs with three to five components. Two major characteristics were observed within these regulatory motifs. Positive configurations, such as feed-forward loops, that favor the propagation of information lead to extended duration of activation of downstream components. Negative configurations that gate signal flow at various levels involve scaffold proteins indicating a spatial dimension in controlling information propagation within the network.

We conducted pseudodynamic analysis of information flow by tracking the propagation of connectivity starting from ligand interaction with the receptor. Connectivity propagation from three key ligands involved in neuronal plasticity, glutamate, norepinephrine and BDNF were analyzed. The rate of connectivity propagation, change in clustering coefficient and the number of motifs recruited per step as connectivity flows downstream were measured. We found that these ligands engage the network at the same rate but with different delays indicating that signal propagation through different classes of pathways may display different network recruitment properties. The shortest delay is for glutamate and longest is for the BDNF signaling. We assembled a series of sub-networks based on allowable connectivity to understand the role of the highly connected nodes. The highly connected nodes are mostly soluble components that can move within the cell. The highly connected nodes reduce the average path length bringing modules together and are involved in the assembly of feed-forward motifs. Thus it appears that the topology of the network facilitates the propagation and maintenance of information within the network to induce long-term changes in the function of cellular machines.