

# Quantitative studies on the responses of signal transduction networks in terms of protein-protein interaction maps

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## ABSTRACT

The complexity of signal transduction networks is overwhelming as evident from the protein-protein interactions resulting from cellular biological studies [1]. This is one of the reasons why the systemic properties emerging from the nonlinear protein-protein interactions are still poorly understood. However, studies on the topology of signal transduction networks have resulted in the concept of subnetworks, i.e. modules, that each perform an emergent task in the global functioning of the regulatory network [2,3]. Some modules amplify or attenuate signal responses whereas others integrate and fine tune multiple signals.

Here we illustrate how to employ the modular character of signaling networks for studies of their responses to external signals. Signal transfer analysis allows for the determination of the global responses of the total network in terms of the responses of its constituent modules [4,5]. Signal transfer analysis is an extension of a rigorous theoretical framework of metabolic control analysis, which led to fundamental insights in control and regulation of biochemical pathways and aided experimental metabolic engineering for the last two decades [6].

Signal transfer analysis allows for the stepwise decomposition of signaling networks into more modules. Hereby the number of protein-protein interactions in the signal transfer analysis description increases gradually which facilitates the understanding of the complex protein-protein interaction maps and how these resulted in the experimentally determined responses of signal transduction networks. Signal transfer analysis will be applied to the glutamine synthetase regulatory network of *Escherichia coli*

and the MAPK pathway emanating from the epidermal growth factor receptor.

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