**504a Elementary Modes and Cybernetic Mechanisms: a Systems-Level Approach for Modeling Biological Regulation**

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Many possibilities have been suggested for how metabolic pathway analysis can be applied to probe the functional capabilities of a given biochemical network. For example, enzyme subsets and excluding reaction pairs are easily detected using elementary mode analysis. Some researchers contend that enzyme subsets are likely to share common regulatory circuits, while excluding reaction pairs are expected to be independently regulated. Despite these qualitative insights linking network topology to regulatory motifs, there has been little progress toward integrating pathway analysis concepts into a quantitative modeling framework that offers prediction of metabolic phenotype based, in part, on structural properties of the network.

This presentation will outline fresh theoretical developments that combine aspects of elementary mode analysis with cybernetic modeling. Cybernetic models represent a particular class of dynamic mathematical models that rely upon optimal control heuristics as surrogates for unknown or incomplete regulatory mechanisms. The new approach views each elementary flux mode (EFM) as a functional unit within the cybernetic model that is capable of accomplishing a specific metabolic conversion. As is customary within the cybernetic modeling framework, cellular metabolism is ascribed certain nutritional objectives that reflect putative evolutionary outcomes. Based on the hypothesis that cellular resources will be optimally allocated, only those EFM's that provide the best return-on-investment will be utilized by the cell. Hence, we can view the regulatory machinery as an analog computer that has evolved heuristic strategies for solving the organism's internal resource allocation problem. The computed control actions serve to modulate the expression and activity of metabolic enzymes that are required to install each individual EFM. The presentation will summarize computational and experimental studies of *E. coli* central carbon metabolism to illustrate how this new class of cybernetic models can be identified from flux and metabolite data. Rational metabolic engineering strategies that involve systematic interrogation and refinement of cybernetic models will also be discussed.