504c Sensitivity of Cybernetic Models to Variability in Microarray Data

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The ‘omics' revolution has accelerated the need for larger and more detailed mathematical descriptions of signaling, regulatory and metabolic networks. Broadly, two classes of metabolic network models have emerged; dynamic models and static stoichiometric models. Cybernetic models are a class of dynamic metabolic network model that use objective based surrogates to capture metabolic regulation and control and to compensate for structural and parametric uncertainty. The ‘cybernetic' aspects of a model are simply optimal control or management problems directing the expression, translation and activity of the enzymes catalyzing network reactions. Cybernetic models have proven successful, over their 20-year lifespan, of predicting complex biological behavior, including physiological multiplicity, the influence of pre-culturing and the impact of genetic and regulatory changes.

A key issue of cybernetic models is the identification of the optimization problem associated with metabolic regulation and control. In this work, a naive formalism for the inference of cybernetic gene expression control problems using DNA Microarrays and the impact of variability in the microarray measurement upon inferred management structure is presented. Using a previously published cybernetic model for Escherichia coli growth on glucose and DNA Microarray measurements for E. coli growth on glucose and acetate, the management structure of E. coli growth on acetate is determined. The resulting model predicted fluxes under the inferred management structure compared well with experiment when perfect information was assumed. A sensitivity analysis to quantify the impact of microarray measurement error upon inferred management structure and estimated flux was performed using a Monte Carlo technique. Results indicate that variability in the microarray data had a large effect upon the inferred management structure and the model estimated flux values. It is concluded that while microarray data holds the potential to identify cybernetic control problems, large variability in the array data may destroy the ability of a naive formalism to correctly infer metabolic management structures.