

## ABSTRACT

DeVilbiss, Frank T. PhD, Purdue University, May 2016. Is Metabolism Goal-Directed? Investigating the Validity of Modeling Biological Systems with Cybernetic Control via Omic Data. Major Professor: Doraiswami Ramkrishna.

Cybernetic models are uniquely juxtaposed to other metabolic modeling frameworks in that they describe the time-dependent regulation of cellular reactions in terms of dynamic “metabolic goals.” This approach contrasts starkly with purely mechanistic descriptions of metabolic regulation which seek to explain metabolic processes in high resolution - a clearly daunting undertaking. Over a span of three decades, cybernetic models have been used to predict metabolic phenomena ranging from resource consumption in mixed-substrate environments to intracellular reaction fluxes of intricate metabolic networks. While the cybernetic approach has been validated in its utility for the prediction of metabolic phenomena, its central feature, the goal-directed control strategy, has yet to be scrutinized through comparison with omic data. Ultimately, the aim of this work is to address the question “Is metabolism-goal directed? through the analysis of biological data. To do so, this work investigates the idea that metabolism is goal-directed from three distinct angles.

The first is to make a comparison of cybernetic models to other metabolic modeling frameworks. These mathematical formulations for intracellular chemical reaction networks range from purely mechanistic, kinetic models to linear programming approximations. Instead of comparing these frameworks directly on the basis of accuracy alone, a novel approach to systems biological model selection is developed. This approach compares models using information theoretic arguments. From this point of view, the model that compresses biological data best captures the most regularity in the data generated by a process. This framework is used to compare the flux

predictions of cybernetic, constraint-based and kinetic models in several case studies. Cybernetic models, in the test cases examined, provide the most compact description of metabolic fluxes. This method of analysis can be extended to any systems biological model selection problem for the purposes of optimization and control.

To further examine cybernetic control mechanisms, the second portion of this dissertation focuses on confronting cybernetic variable predictions with data that is representative of enzyme regulation. More specifically, the dynamic behavior of cybernetic variables,  $u_i$ , which are representative of enzyme synthesis control are matched with gene expression data that represents the control of enzyme synthesis in cells. This comparison is made for the model system of cybernetic modeling, diauxic growth, and for prostaglandin (PG) metabolism in mammalian cells. Via analysis of these systems, a correlation between the dynamic behavior of cybernetic control variables and the true mechanisms that guide cellular regulation is discovered. Additionally, this result demonstrates potential use of cybernetic variables for the prediction of relative changes in gene expression levels.

The last approach taken to test the veracity of cybernetic control is to develop a technique to mine objective functions from biological data. In this approach, returns on investment (ROIs) for various pathways are first established through simultaneous analysis of metabolite and gene expression data for a given metabolic system. Following this, the ROIs are used to determine a metabolic systems observed “goal signal.” Gene expression data is then mined to select genes that show expression changes that are similar to the goal signal’s behavior. This gene list is then analyzed to determine enriched biological pathways. In the final step, these pathways are then surveyed in the literature to establish feasible metabolic goals for the system of interest. This method is applied to analyze diauxic growth and prostaglandin systems and generates objective functions that are relevant to known properties of these metabolic networks from the literature. An enhanced understanding of metabolic goals in mammalian systems generated by this work reveals the potential utility of cybernetic modeling in new directions related to translational research.

Overall, this investigation yields support of the notion of dynamic metabolic goals in cells through comparison of metabolic modeling approaches and through the analysis of omic data. From these results, a lucid argument is made for the use of goal-directed modeling approaches and a deeper understanding of the optimal nature of metabolic regulation is gained.