ABSTRACT

Aboulmouna, Lina M. Ph.D., Purdue University, October 2020. Towards Cybernetic Modeling of Biological Processes in Mammalian Systems—Lipid Metabolism in the Murine Macrophage. Major Professor: Doraiswami Ramkrishna

Regulation of metabolism in mammalian cells is achieved through a complex interplay between cellular signaling, metabolic reactions, and transcriptional changes. The modeling of metabolic fluxes in a cell requires the knowledge of all these mechanisms, some of which may be unknown. A cybernetic approach provides a framework to model these complex interactions through the implicit accounting of such regulatory mechanisms, assuming a biological "goal". The goal-oriented control policies of cybernetic models have been used to predict metabolic phenomena ranging from complex substrate uptake patterns and dynamic metabolic flux distributions to the behavior of gene knockout strains. The premise underlying the cybernetic framework is that the regulatory processes affecting metabolism can be mathematically formulated as a cybernetic objective through variables that constrain the network to achieve a specified biological "goal".

Cybernetic theory builds on the perspective that regulation is organized towards achieving goals relevant to an organism's survival or displaying a specific phenotype in response to a stimulus. While cybernetic models have been established by prior work carried out in bacterial systems, we its applicability to more complex biological systems with a predefined goal. We have modeled eicosanoid, a well-characterized set of inflammatory lipids derived from arachidonic acid, metabolism in mouse bone marrow derived macrophage (BMDM) cells stimulated by Kdo2-Lipid A (KLA, a chemical analogue of Lipopolysaccharide found on the surface of bacterial cells) and adenosine triphosphate (ATP, a danger signal released in response to surrounding cell death) using cybernetic control variables. Here, the cybernetic goal is inflammation; the hallmark of inflammation is the expression of cytokines which act as autocrine signals to stimulate a pro-inflammatory response. Tumor necrosis factor (TNF)-α is an exemplary pro-inflammatory marker and can be designated as a cybernetic objective for modeling eicosanoid—prostaglandin (PG) and leukotriene (LK)—metabolism. Transcriptomic and lipidomic data for eicosanoid biosynthesis and conversion were obtained from the LIPID Maps database. We show that the cybernetic model captures the complex regulation of PG metabolism and provides a reliable description of PG

formation using the treatment ATP stimulation. We then validated our model by predicting an independent data set, the PG response of KLA primed ATP stimulated BMDM cells.

The process of inflammation is mediated by the production of multiple cytokines, chemokines, and lipid mediators each of which contribute to specific individual objectives. For such complex processes in mammalian systems, a cybernetic objective based on a single protein/component may not be sufficient to capture all the biological processes thereby necessitating the use of multiple objectives. The choice of the objective function has been made by intuitive considerations in this thesis. If objectives are conjectured, an argument can be made for numerous alternatives. Since regulatory effects are estimated from unregulated kinetics, one encounters the risk of multiplicity in this regard giving rise to multiple models. The best model is of course that which is able to predict a comprehensive set of perturbations. Here, we have extended our above model to also capture the dynamics of LKs. We have used migration as a biological goal for LK using the chemoattractant CCL2 as a key representative molecule describing cell activation leading to an inflammatory response where a goal composed of multiple cybernetic objectives is warranted. Alternative model objectives included relating both branches of the eicosanoid metabolic network to the inflammatory cytokine TNFα, as well as the simple maximization of all metabolic products such that each equally contributes to the inflammatory system outcome. We were again able to show that all three cybernetic objectives describing the LK and PG branches for eicosanoid metabolism capture the complex regulation and provide a reliable description of eicosanoid formation. We performed simulated drug and gene perturbation analyses on the system to identify differences between the models and propose additional experiments to select the best cybernetic model.

The advantage to using cybernetic modeling is in its ability to capture system behavior without the same level of detail required for these interactions as standard kinetic modeling. Given the complexity of mammalian systems, the cybernetic goal for mammalian cells may not be based solely on survival or growth but on specific context dependent cellular responses. In this thesis, we have laid the groundwork for the application of cybernetic modeling in complex mammalian systems through a specific example case of eicosanoid metabolism in BMDM cells, illustrated the case for multiple objectives, and highlighted the extensibility of the cybernetic framework to other complex biological systems.