A Cybernetic Approach to Modeling Lipid Metabolism in Mammalian Cells

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Highlights

- **C**ybernetic metabolic objectives can be used to describe regulation in mammalian systems.
- **C**ybernetic models captures metabolic perturbations via various effectors including drugs.
- Macrophage cells tune their generation of various prostaglandins to maximize rate of TNF-a.

Keywords
Metabolic Modeling, Omic Data, Cybernetic Modeling, Metabolic Objective Functions

1. Introduction

Metabolism is regulated by a number of factors in the cell. The concerted action of metabolism and regulation gives rise to the cellular phenotype or cellular outcome behavior. The cybernetic approach developed by our group assumes a goal and evolves the dynamics of the system under regulation to determine how each of the variables (e.g., metabolite concentrations) evolve over time, and how the metabolite fluxes are regulated.

The key advantage of cybernetic descriptions of cellular regulation is that they capture the molecular phenomena that control metabolic fluxes in the form of an intuitive regulatory principle. From the cybernetic perspective, regulatory mechanisms at the molecular level are not isolated events. Regulation is a cooperative cascade of molecular incidents that are coordinated to enhance a cell's survival. Regulatory goals, such as maximizing growth [1] or carbon uptake rate [2], provide a causality driven basis for the regulation of individual chemical events. In the absence of high resolution, dynamic data for all cellular events that modulate metabolism, cybernetic assumptions of regulation offer a significant advantage in that they are simple and can robustly predict metabolic phenomena given an appropriate objective function.

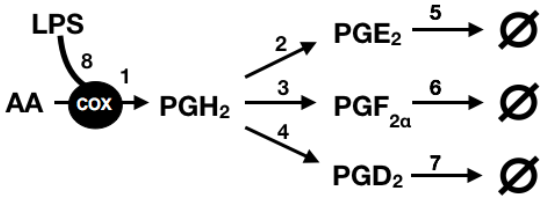
While cybernetic models have focused on bacterial systems in the past, we presently adapt this framework to model the dynamic behavior of prostaglandin (PG) formation in a mammalian cell line, RAW 264.7 macrophages. Several kinetic descriptions of PG formation precede this work [3, 4], but none take into account the regulatory phenomena present in PG formation. Our application of cybernetics to macrophages provides a quantitative model of eicosanoid metabolism initiated with the input of arachidonic acid (AA) and resulting in the inflammatory outcome represented by TNF-alpha.

2. Methods

To describe the time-dependent formation of PGs, a cybernetic model is generated. This description approximates the conversion of AA into intermediate product, prostaglandin H_2 (PGH_2) and its subsequent conversion into downstream prostaglandin E2 (PGE_2), prostaglandin F_{2a} (PGF_{2a}), and prostaglandin D_2 (PGD_2). In this simple network of PG formation, the main focus is on how PGH_2 is converted into downstream PGs because the regulation of this branch point involving the synthesis of three separate products represents a central decision point in the metabolic system (figure 1A).

In using cybernetic arguments to model PG formation (figure 1B), we are assuming that these products are formed in varying amounts related to their ability to help the cell achieve its inflammatory objective. The production of PGs that have a stronger relationship with the goal of the system will be upregulated while the pathways for those PGs which have a lesser relationship with the objective function will be downregulated. The network generates metabolites in order to accomplish some goal which is embedded into the model using cybernetic regulation.

A



B

$$\frac{dPGH_2}{dt} = r_{AA\rightarrow PGH_2} - \sum_{i=1} v_i e_i r_{PGH_2\rightarrow PG_i}$$

$$\frac{dPG_i}{dt} = v_i e_i r_{PGH_2\rightarrow PG_i} - r_{PG_i\rightarrow\emptyset}$$

$$\frac{de_i}{dt} = \alpha_i + u_i \frac{k_{E,i} PGH_2}{K_{E,i} + PGH_2} - \beta_i e_i$$

Figure 1: A) Network for the metabolism and signaling pathway of lipopolysaccharide (LPS) stimulation that leads to the catalysis of PGs from AA via the enzyme COX (cyclooxygenase). B) In addition to changes in metabolites, the relative changes in enzyme level e_i (modeled as a function of constitutive formation, induced formation, and degradation) for each pathway are also modeled with ordinary differential equations. Regulation is implemented via u and v, the cybernetic control variables. The dynamic variable u_i represents the regulation of induced enzyme formation, and v_i modulates enzyme activity which typically occur through allosteric mechanisms.

3. Results and discussion

After fitting parameters to two conditions (i.e., the control and KLA treatment conditions), the model provided the fits which are shown in figure 2. In the modeling of metabolism of AA through the COX pathway, the lipid metabolic pathways upstream of AA and the signaling pathways that regulate AA metabolism were not modeled due to the unknown factors and complexity. Hence, we did not fit the AA data in the above optimization problem and used AA profiles as representations of the different conditions. Also, it is evident that the model correctly explains the evolution of the metabolite concentrations for the different conditions involved in the fit. The control shows a relatively low rate of prostaglandin formation. The KLA treatment shows a good agreement with all prostaglandin products generated. The kinetics of the model can be cross-validated using additional treatment conditions.

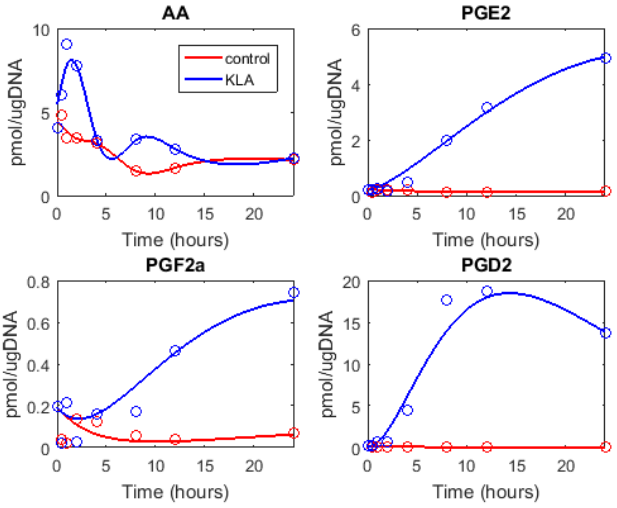


Figure 2: Time evolution of metabolite concentrations (pmol/ugDNA) for prostaglandin system. Each condition is distinguished by color with the control case in red and KLA treatment in blue. Experimental data points for each of these conditions are in the same color.

4. Conclusions

Cybernetic models are a robust description of metabolite formation and can be used to predict perturbations to metabolism viavarious effectors including drugs. Having a more reliable description of PG formation is useful in that it can provide a more predictive description of the action of inhibitory drugs. It is the goal of this work to offer proof of concept that return on investment can be broadened to describe objective functions in complex multi-cellular systems and have applications in predicting the response of metabolic networks to drugs.

This work, for the first time, develops the idea that cybernetic metabolic objectives can be used to describe the regulation of signaling systems in mammalian metabolism. It yielded a model describing PG synthesis that is capable of predicting both metabolites and the relative changes in gene expression. This model will be used to provide robust predictions of how drugs that inhibit PGH_2 formation alter the downstream generation of PGs which also marks the first time that cybernetic models are explicitly used for pursuits in translational research.

References

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