Cracking the Code of Metabolic Regulation: Optimal Control and Reinforcement Learning of Regulation and Enzyme Activities

Samuel Britton¹, Mark Alber¹, William Cannon¹,²

¹Department of Mathematics, University of California Riverside, Riverside, CA
²Physical and Computational Sciences Directorate and Biological Sciences Division, Pacific Northwest National Laboratory, Richland, WA

Overview

Experimental measurement or computational inference/prediction of the enzyme regulation needed in a metabolic pathway is hard problem. Consequently, regulation is known only for well-studied reactions of central metabolism in various model organisms. In this study, we use statistical thermodynamics and metabolic control theory as a theoretical framework to calculate enzyme regulation policies for controlling metabolism. A reinforcement learning approach is utilized to learn optimal regulation policies that match physiological levels of metabolites while maximizing the entropy production rate and minimizing the heat loss. The learning takes a minimal amount of time, and efficient regulation schemes were learned that either agree with theoretical calculations or result in a higher cell fitness using heat loss as a metric. We demonstrate the process on four pathways in the central metabolism of Neurospora crassa (gluconogenesis, glycolysis-TCA, Pentose Phosphate-TCA, and cell wall synthesis) that each require different regulation schemes.

Prediction of Dynamics & Regulation

A new approach to the law of mass action does not require rate parameters but instead uses chemical potentials (1). Due to the statistical formulation of the theory, the approach can directly integrate metabolomics and proteomics data.

◆ Governing Equations

Chemical Reaction: 

\[ \frac{\Delta C}{\text{time}} = \frac{\Delta B}{\text{time}} - \frac{\Delta C}{\text{time}} \]

Mass Action Reaction Flux: 

\[ J_{\text{mass action}} = k \frac{A_n}{A_n} \]

Marcelin-De Donder Equation: 

\[ J_{\text{marcelin}} = k \frac{A_n}{A_n} \]

1910 Marcelin Equation: 

\[ J_{\text{1910}} = c_i \left( K_i Q_i \right) - c_i \left( K_i Q_i \right) \]

The Marcelin Equation sets each of the decay rates of the forward and reverse forces to the same rate. Assuming the same decay rate for all reactions removes any kinetic bottlenecks in phase space of the system such that the dynamics are governed only by the thermodynamics and the energy surface is convex.

◆ Equivalent Optimization

Reconstruction of the flux allows an optimization routine to a steady state as well as the usual ODE solver approach. Since the flux can be rewritten using a maximum entropy assumption as the Marcelin Equation, a steady state is achieved by solving the coupled system

\[ \frac{dn_i}{dt} = S^T J \]

\[ = S^T \left( KQ - KQ \right) \]

Given appropriate fixed boundary values for metabolites, the system has a unique solution. Steady state concentrations and fluxes can be gleaned by solving a convex optimization problem:

\[ \min \left[ S^T \left( KQ - KQ \right) \right] \]

The predicted concentrations are a maximum entropy prediction.

◆ Adjust Enzyme Activities using Metabolic Control Analysis

Deterministic Regulation. Postulating a linear response, the choice of which reaction is to be regulated at a given steady state can be solved as an optimal control problem using Metabolic Control Analysis. Concentration control coefficients, \( C_j = \frac{\partial \Delta c_j}{\partial x_j} \), represent the correlated sensitivity of the j-th metabolite and the i-th activity and can predict beneficial regulation. Each reaction is valued by normalizing the potential change in metabolites by the current value

\[ \Delta c_j = \sum_{i=1}^{n_j} \left[ \max \left( C_j, 0 \right) \right] \]

Reactions chosen to be regulated maximize \( \Delta c_j \). The activity \( a_i \) for reaction \( j \) is then adjusted and a new steady state solution is found,

\[ \min \left[ S^T \left( KQ - KQ \right) \right] \]

Enzyme activities continue to be adjusted until \( \Delta S_{\text{eq}} \leq 0 \).

◆ Agreement with Experiment

Experiment Simulation

Reinforcement Learning Based Regulation

◆ Calculation of Regulation

MCA presumes that the concentrations will change linearly with enzyme activity, but this is not necessarily true. Reinforcement Learning (RL) can be used to learn optimal regulation instead.

Regulation is applied to reactions by changing the scalar valued activity of the j-th enzyme, \( a_j \in [0,1] \), where activity values of 0 and 1 represent complete reaction regulation and no enzyme regulation respectively. The activity for each reaction \( j \) is applied as a multiplier to the net reaction flux.

- Net reaction flux: \( f_j = a_j \left( K_i Q_j^i - K_j Q_j \right) \).
- Regulation step size: \( \Delta a_j = a_j \frac{K_i Q_j^i}{N} \sum_{k=1}^{n_j} K_k S_k f_j \).
- Linear stability matrix: \( A = \pi \sum_{k=1}^{n_j} \frac{a_j}{N} \frac{\partial f_j}{\partial a_j} \).

◆ Learning Regulation

The agent (Figure 1) is meant to determine an optimal regulation policy that results in a maximal reward. This is achieved by utilizing n-step SARSA algorithm and neural network function approximation for the value function.

- States are represented as a set of regulation values: \( a = [a_1, ..., a_n] \).
- Actions are defined by advancing a single MCA calculated step.

Regulation predictions for both metabolic control (red ’X’) and RL (grey lines) based methods are shown for each reaction (Figure 3). Corresponding entropy production rates or cell fitness from the respective methods are compared (Figure 2).

References