379b Discovery and Analysis of Biological Control Laws

Jamey D. Young and Doraiswami Ramkrishna

Unlike other natural systems, biological systems are primarily governed by feedback regulation occurring at the transcriptional and translational levels, as well as by allosteric control of enzyme activities. Accounting for these regulatory actions in a rational manner is the main challenge faced by modelers. The traditional kinetic modeling approach involves postulating chemical mechanisms that reflect the various regulatory controls, which may then be translated into inhibition and activation terms within the appropriate kinetic expressions. Unfortunately, this approach requires a detailed knowledge of regulatory mechanisms and molecular interactions (which is rarely available) and leads to a rapidly expanding set of kinetic parameters. The cybernetic modeling approach, on the other hand, views the entire biological system from an evolutionary perspective. Based on a general understanding of the nutritional objectives that an organism must satisfy in order to grow and survive, cybernetic control laws are derived that lead to optimal utilization of the organism's metabolic capabilities. It has been shown that, in many cases, these cybernetic laws provide excellent approximations to the actual system response. Accounting for regulatory control actions in this manner greatly reduces model complexity and leads to simulations that are stable and reliable over a wide range of possible phenotypes.

The chief objective of this presentation is to revisit the cybernetic modeling framework of Ramkrishna and coworkers from a fresh viewpoint. The exercise is significant in elucidating the exact nature of the optimality implied by previous cybernetic control laws. Two optimal laws have appeared in the foregoing cybernetic modeling literature. The first of these, concerned with regulation of enzyme synthesis, has been referred to as the Matching Law, while the second, associated with control of enzyme activity, has been termed the Proportional Law. These laws were originally derived using relatively crude arguments, which we now attempt to refine. Besides providing clarity, the current development is prerequisite to the offshoot of generalizations leading to new cybernetic laws or extended applicability of existing laws. Moreover, this treatment enables a systematic comparison of alternate control policies that result from differing notions of optimality, thereby providing a context in which the unique properties of the Matching and Proportional Laws can be fully discerned and appreciated. Computational results are presented that summarize the relative merits of several suggested control laws in describing the growth dynamics of mixed-substrate bacterial cultures. Depending on the aggressiveness of the control, the predicted behavior can range from simultaneous uptake to sequential uptake of the available nutrients. Monte Carlo simulations designed to probe the response of each control law under varying ecological conditions are also discussed. These results shed light on the robustness properties associated with each candidate control law.