

504b A Hybrid Model of Metabolic Networks: Cybernetic Approach with Elementary Mode Analysis

Jin Il Kim

To formulate the model equations of cell metabolism, the effect of metabolic regulation should be taken into account. Flux balance methods depend on combining information on external fluxes, stoichiometric constraints and optimization strategies to calculate all internal fluxes and the yields of biomass and fermentation products. However, in view of their dependence on specification of external fluxes, they do not represent a predictive approach to metabolic systems analysis. On the other hand, the cybernetic framework of Ramkrishna and coworkers approaches metabolic modeling by postulating that regulation is the consequence of the cells' attempt to make frugal use of their internal resources to optimally affect the syntheses of enzymes catalyzing the various chemical reactions. The early cybernetic models, which had relatively coarse structure, were not equipped to predict internal metabolite levels or various fermentation products. In this presentation, we present the cybernetic approach with the flux balance approach to extract its predictive capabilities. The objective of this effort is to examine the effectiveness of the coarse cybernetic models to predictive external fluxes and to evaluate the model's capacity to describe observed dynamic behavior. The hybrid model consists of two following frameworks: 1) the optimal modes for internal fluxes 2) the cybernetic model of Baloo and Ramkrishna (1991) for external fluxes. The metabolic network of anaerobic *E.coli* was selected as a sample network. The cybernetic variables are the same as those of Baloo and Ramkrishna (1991), and the optimal modes for growth and maintenance were selected among all elementary modes of GJT001 wild type strain and YBS121 acetate knock-out strain by proper criteria. The hybrid model predicts growth and fermentation behavior very close to the experimental data, except the succinate production of GJT001 and ethanol production of YBS121. That can conceivably be caused by adding another optimal mode to the cybernetic framework for succinate/ethanol production. Another metabolic network of aerobic *Klebsiella pneumoniae* was tested for evaluating the maintenance effect at the low growth rate situation. Stepping the dilution rate up and down in a continuous culture, the impact of the resource limitation and increment of maintenance effect at the low concentration of glucose was successfully simulated.

Reference:

Baloo, S., Ramkrishna, D., 1991. Metabolic regulation in bacterial continuous cultures: I. *Biotechnology and Bioengineering* 38 (11), 1337-1352.