

Invited Talk 2.4

CONSTRAINTS AND REGULATION OF METABOLIC NETWORKS

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Abstract

The influence of the high intracellular concentration of macromolecules on cell physiology is increasingly appreciated, but its impact on system-level cellular functions remains poorly quantified. To assess its potential effect, we developed a flux balance model of *Escherichia coli* cell metabolism that takes into account a systems-level constraint for the concentration of enzymes catalyzing the various metabolic reactions in the crowded cytoplasm. We demonstrate that the model's predictions for the relative maximum growth rate of wild-type and mutant *E. coli* cells in single substrate-limited media, and the sequence and mode of substrate uptake and utilization from a complex medium are in good agreement with subsequent experimental observations. Using this model we also predict a global metabolic reorganization in *E. coli* cells growing in glucose when they are shifted from low to high growth rates. The predictions are in part confirmed by flux measurements of central metabolic reactions. Subsequent enzyme activity and mRNA expression measurements indicate that the dominant regulatory mechanism controlling switch is constituted by changes in the activity of a few key enzymes in the *E. coli* central metabolism. These results suggest that molecular crowding represents a bound on the achievable functional states of metabolic networks, and indicate that models incorporating this constraint can systematically identify alterations in cellular metabolism activated in response to environmental change.

Biography

Zoltán Oltvai is an Associate Professor of Pathology and Assistant Director of the Division of Molecular Diagnostics. His research interest is in the area of systems biology, focusing on how the functional organization of molecular interaction networks define and constrain cellular functions.