Flux Analysis Uncovers Key Role of Functional Redundancy in Formaldehyde Metabolism

Christopher J. Marx[1†], Stephen J. Van Dien[3], Mary E. Lidstrom[1,2*]

Departments of Microbiology[1] and Chemical Engineering[2], University of Washington, Seattle, WA 98195, USA; [3]United Metabolics, 804 N. 43rd St., #5, Seattle, WA 98103 USA.

[†]Present address: Department of Microbiology & Molecular Genetics, Michigan State University, East Lansing, Michigan 48824, USA. marxchri@msu.edu

*To whom correspondence should be addressed: E-mail: lidstrom@u.washington.edu

Summary

Background. Genome-scale analysis of predicted metabolic pathways has revealed the common occurrence of apparent redundancy for specific functional units, or metabolic modules. In many cases, mutation analysis does not resolve function and instead direct experimental analysis of metabolic flux under changing conditions is necessary. In order to use genome sequences to build models of cellular function, it is important to define function for such apparently redundant systems. *Methodology/Principal Findings.* Here we describe direct flux measurements to determine the role of redundancy in three modules involved in formaldehyde assimilation and dissimilation in a bacterium growing on methanol. A combination of deuterium and ^{14}C labeling was used to measure the flux through each of the branches of metabolism for growth on methanol during transitions into and out of methylotrophy. The cells were found to differentially partition formaldehyde amongst the three modules depending on the flux of methanol into the cell. A dynamic mathematical model demonstrated that the kinetic constants of the enzymes involved are sufficient to account for this phenomenon. *Conclusions/Significance.* We demonstrate the role of redundancy in formaldehyde metabolism and have uncovered a new paradigm for coping with toxic, high-flux metabolic intermediates: a dynamic, interconnected metabolic loop.