

Propionate response in *Salmonella enterica* serovar typhimurium: integration of metabolomics and biosensor data for model development

Kenneth J. Kauffman^{1,2}, Jack Newman², Matthew Garcia², and Jay D. Keasling²

¹University of California
Chemical & Environ Engr
A242 Bourns Hall
Riverside, CA 92521
kkauffma@ucr.edu

²University of California
Chemical Engineering
401 Latimer Hall
Berkeley, CA 94712
keasling@socrates.berkeley.edu

Like many other bacteria, *Salmonella enterica* serovar typhimurium experiences proton gradient disruption in the presence of propionate. To respond to this stress, the cell has evolved a consumption network that reacts propionate with oxaloacetate to form 2-methyl citrate (2MC). 2MC is then broken down into succinate and pyruvate. The net result of this reaction is the conversion of propionate to pyruvate, the consumption of one high energy phosphate bond, and the generation of two reducing equivalents. The PRP operon encodes most of the proteins that compose this pathway. 2MC appears to serve as a sensor molecule for the PRP operon. Here we describe the construction of a GFP based biosensor for the activity of the PRP promoter region. This biosensor was then used to track the time course of fermentations of *Salmonella enterica* serovar typhimurium grown on lactate minimal media with pulses and spikes of propionate.

Several interesting features in the dynamics of the GFP response indicate that the behavior of the pathway exhibits interesting control features. For example, preliminary spike data indicates there may be on-off or wind-up control present on the pathway. The dynamics of this response indicate a time constant several times faster than the doubling time of the cell. To better understand the underlying situation and to be able to better relate the biosensor output to the underlying phenomena of the bioreactor, we measured the intracellular concentrations of several metabolites. As the pathway responding to propionate directly impacts the citric acid cycle, we measured propionate, oxaloacetate, succinate, pyruvate, acetyl-CoA, free CoA, propionyl-CoA, succinyl-CoA, ATP and ADP levels. Using experimental results from multiple inputs, a mathematical model capturing the dynamics of the various responses was proposed and identified. Using the preliminary model results, additional experiments are being proposed to further elucidate the type of control present in the cellular system.