Transient Bimodality Generates an Anticipatory Regulatory Strategy that Enhances Adaptation to Combinatorial Environments

Hana El-Samad
Department of Biochemistry and Biophysics, California Institute for Quantitative Biosciences, University of California San Francisco, San Francisco, CA 94158, USA

Delineating the strategies used by cells to contend with combinatorial environments is crucial for our understanding of cellular regulatory organization. When microorganisms are presented with two carbon sources, they consume the carbon substrate that supports the highest growth rate (e.g. glucose) before metabolizing the secondary carbon source (e.g. galactose). This is widely known as the Monod model. A sequential pattern of sugar utilization has traditionally been attributed to the transcriptional repression of the secondary sugar pathway, which is activated only upon depletion of the preferred carbon source. In this work, we challenge this notion. *Saccharomyces cerevisiae* cells presented with glucose and galactose consume glucose before galactose. However, contrary to Monod's model, we demonstrate that the galactose regulatory pathway (GAL) is activated in a fraction of the cell population hours before glucose is fully consumed. The fraction of activated cells is tuned by the quantities of the two sugars in the environment. Pre-emptive activation reduces the time required to transition between the two metabolic programs and provides a fitness advantage. These data not only define a new paradigm for response to combinatorial carbon sources, but also suggest that regulated diversification of a population into distinct regulatory states may provide a crucial kinetic advantage in competitive environments.

.