SYSTEMS BIOLOGY

Timing is everything

Even a well-crafted comedic performance will leave an audience cold unless the timing is right. It now emerges that, like comedic expression on stage, gene expression in metabolic pathways also needs to be well-timed to be effective.

Alon Zaslaver and colleagues studied the timing and strength of the expression of genes in a well-characterized type of pathway: amino-acid biosynthesis (AAB) in *Escherichia coli*. They developed an ingenious system for monitoring gene expression that involved cloning the promoter regions of ~50% of all known *AAB* genes into plasmids, upstream of reporter genes (*Lux* or *GFP*). By using an automated multiwell fluorimeter, the authors could monitor promoter activity in these 52 reporter strains every few minutes to an accuracy of 10%.

Zaslever *et al.* were able to address sophisticated questions about the dynamics of gene expression in the AAB pathway. First, they showed that, as might be expected, excess amounts of an individual amino acid in the medium led the genes in that amino acid's biosynthetic pathway to be downregulated. However, the really interesting results came when they examined reactivation of such pathways when the corresponding amino acids were removed.

In the three amino-acid systems that were studied in detail — arginine, methionine and serine — the expression of genes in unbranched pathways was reactivated in the same order as they were positioned in the pathway: that is, the first gene in the pathway was also the first to be reactivated, and so on. Zaslever and colleagues also showed another striking correlation between functional hierarchies and gene-expression patterns: in all three cases, the closer a gene was to the beginning of the pathway, the higher was its maximal level of expression.

To explain these remarkable patterns, the authors went on to mathematically model enzyme production in such unbranched 'production pipeline'-style pathways. Their model clearly showed that the hierarchies in the timing and magnitude of gene expression in these pathways minimized the time that was required and the metabolic cost of producing the final enzyme. Higher and earlier expression of the genes at the top of the pathway provides a boost in the intial enzymes required, allowing a faster response to withdrawal of the amino acid.

The results of Zaslever *et al.* are fascinating just for the insight that they provide into the delicate regulation of amino-acid synthesis in bacteria. Experiments such as these might be as important to the development of systems biology as similarly elegant experiments in *E. coli* were to that of molecular biology and genetics.

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References and links

ORIGINAL RESEARCH PAPER Zaslaver, A. *et al.* Just-in-time transcription program in metabolic pathways. *Nature Genet.* **36**, 486–491 (2004)

FURTHER READING Barabasi, A.-L. & Oltvai, Z. N. Network biology: understanding the cell's functional organization. *Nature Rev. Genet.* **5**, 101–113 (2004)

WEB SITE
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