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GENE NETWORKS

Network analysis gets dynamic

Biological networks are highly dynamic, and respond to changing conditions in myriad ways. Studies aimed at understanding how these networks contribute to cellular function have uncovered motifs — patterns of interactions between genes — that are abundant within biological networks. But the information given by these motifs is static and only tells us the possible routes within a network, not how and when they are used. A new study describes a novel analytical framework that reflects the dynamic nature of networks, and uses it to provide insights into the transcriptional regulation of yeast metabolism.

Chechik *et al.* used a model of the *Saccharomyces cerevisiae* metabolic network that consists of 1,181 reactions catalyzed by 598 enzymes. After identifying static network motifs, they then detailed possible 'activity motifs' by using expression data from 63 published and 13 original time-course experiments. Activity motifs place functional data over network motifs to identify which interactions are activated in defined conditions. Here, data detailing the timing of transcriptional onset after a sudden change in environmental conditions were placed over motifs in the *S. cerevisiae* metabolic network.

The authors identified numerous motifs that they called timing activity motifs (TAMs). Whereas a network motif identifies the enzymes in a pathway, a TAM describes the order in which these enzymes are expressed. The most common TAM identified was the forward-activation TAM, in which the enzymes are transcribed in the order in which they are used in a pathway — an efficient use of transcriptional resources. Surprisingly, the backward-activation TAM was also enriched in several conditions. The authors suggest that this TAM might be used to remove an end product that would otherwise interfere with the pathway or be toxic to the yeast cells. In addition, forward and backward repression TAMs were identified — an entirely new type of motif. Importantly, the authors provide evidence that TAMs operating at the transcriptional level are also relevant at the level of protein abundance.

Looking at the distribution of TAMs across the network, most were found in central carbon metabolism (CCM), suggesting that timing of gene expression for enzymes in CCM is finely tuned. The authors also highlight an evolutionary insight: enzymes associated with common TAMs have undergone more gene duplication and loss events than other metabolic enzymes. A potential explanation for this is that higher levels of copy number variation for these genes makes them more sensitive to environmental change, necessitating tight regulation.

Although their analyses revealed that timing of transcription within the metabolic network is often highly controlled, the mechanism for this control could not be elucidated through TAMs alone. To address this, the authors mapped the binding affinity of several transcription factors (TFs) onto network motifs to define binding activity motifs (BAMs). There was significant overlap between forward-activation TAMs and BAMs, suggesting that tuning of TF binding affinities is important in the temporal regulation of transcription. This supports the notion of a 'pre-programmed' transcriptionally regulated response of metabolic networks during times of sudden environmental change.

The results from the timing analysis reflect both transcription and degradation of mRNA; disentangling the two influences is an area for future study. The framework could also be used to elucidate the roles of dynamic network activity in a broad range of cellular functions in yeast and in other organisms. In addition, activity motifs can be applied to numerous types of different networks, including *cis*-regulatory and signalling networks, or even social and world-wide-web networks.

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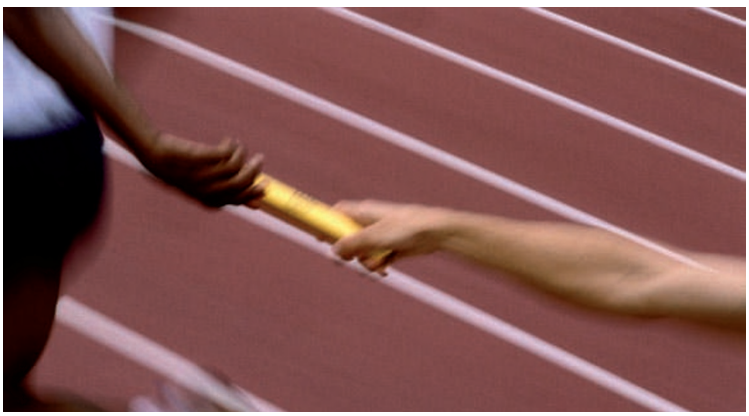

ORIGINAL RESEARCH PAPER Chechik, G. *et al.* Activity motifs reveal principles of timing in transcriptional control of the yeast metabolic network. *Nature Biotechnol.* 26 Oct 2008 (doi:10.1038/nbt.1499)

FURTHER READING Alon, U. Network motifs: theory and experimental approaches. *Nature Rev. Genet.* **8**, 450–461 (2007)