GENE REGULATION

Modelling by building blocks

The recent explosion in the rate of discovery of transcription-factor binding sites has led to a need to understand how these sites affect gene expression. A significant contribution towards understanding how promoter binding sites function together in different combinations has been provided by a new thermodynamic model that can accurately predict the relationship between promoter sequence and expression output.

Thermodynamic models of gene expression are based on the assumption that the level of gene expression is proportional to the equilibrium probability that RNA polymerase is bound to the promoter of interest. These models have previously been used to describe gene expression in small sets of eukaryotic genes; however, there have been concerns that these models are subject to over-fitting owing to the small number of

genomic promoters that have been studied in these systems. The use of synthetic gene promoters avoids this limitation — any promoter sequence can be created and analysed, thus allowing models to be assessed using most of the possible combinations of regulatory elements.

Cohen and colleagues constructed synthetic promoter libraries in the yeast *Saccharomyces cerevisiae*. Each promoter consisted of random combinations of three or four transcription-factor binding sites (or 'building blocks'), and its activity was assayed by monitoring the expression of a downstream reporter gene, yellow fluorescent protein (*YFP*). Over 2,800 promoters using combinations of 18 different building blocks were analysed — this allowed the authors to test their general thermodynamic model using many combinations of regulatory elements.

The model describes a large amount of the variation in gene expression that is directed by different promoter sequences, and accounts for more of this variation than previously described models of gene regulation. Moreover, the model accurately described phenomena such as cooperativity between transcription-factor binding sites and the effects of weak binding sites. The authors also applied their model to

the *S. cerevisiae* genome: here they were able to identify a number of genes that were regulated by the Mig1 transcription factor but that were not previously known to be Mig1 targets (because they lack a strong Mig1 binding site in their promoters). This suggests that the model can be extended to predict novel transcription factor–gene interactions.

The thermodynamic model developed by the authors assumed that gene regulation is completely controlled by simple DNA–protein and protein–protein interactions at the promoter, and does not take enzymatic interactions into account. The results of this study therefore have general implications for understanding gene regulation: they suggest that events such as chromatin modification and polymerase phosphorylation are downstream of the primary DNA and protein interactions and might therefore play minor parts in the relationship between promoter sequence and gene expression.

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ORIGINAL RESEARCH PAPER Gertz J. et al. Analysis of combinatorial cis-regulation in synthetic and genomic promoters. *Nature* 23 Nov 2008 (doi: 10.1038/nature07521)

FURTHER READING Boone C. et al. Exploring genetic interactions and networks with yeast. *Nature Rev. Genet.* 8, 437–449 (2007).