Nature Reviews Genetics | AOP, published online 2 March 2010; doi:10.1038/nrg2768

TRANSCRIPTIONAL REGULATION

Non-cooperative transcriptional control

Transcription is thought to operate in a digital (either on or off) manner, which is regulated by the cooperative binding of transcription factors. However, this simplistic model has been challenged by the recent demonstration that graded transcriptional control can occur through the non-cooperative binding of a transcription factor, which suggests that different modes of transcriptional control may be important in different situations.

Giorgetti and colleagues studied transcriptional regulation by the inflammatory transcription factor nuclear factor-κB (NF-κB). In a genome-wide analysis of NF-κB binding sites in the human genome, they found that clusters of NF-κB binding sites are a common occurrence in the upstream regions of NF-κB target genes, including NF-κB family members themselves and negative regulators of NF-κB activity.

What effect do these clusters have on the NF-κB transcriptional response? The authors found that genes with clustered NF-κB binding sites responded to an increasing gradient of nuclear NF-κB concentration by gradually increasing transcription — an analogue response rather than a digital one.

The authors then designed a thermodynamic model that incorporated a limited number of parameters to explain the NF-κB-mediated transcriptional regulation by homotypic clusters of NF-κB binding sites, and compared it with the experimental data. The model was consistent with a scenario in which NF-κB binds independently to each binding site within the cluster, therefore promoting RNA polymerase II recruitment in an additive manner.

Why might this mode of non-cooperative transcriptional regulation be necessary? The authors speculate that an increased number of transcription factor-binding sites might enable a more sensitive transcriptional response to changes in transcription factor concentration or might allow for greater transcriptional robustness. In addition, the needs of different biological processes may differ and require transcriptional outputs to be tailored accordingly; for example, digital transcriptional responses may be used during development to create tightly defined anatomical borders, whereas environmental challenges might require graded analogue responses that accurately reflect the strength of the stimulus.

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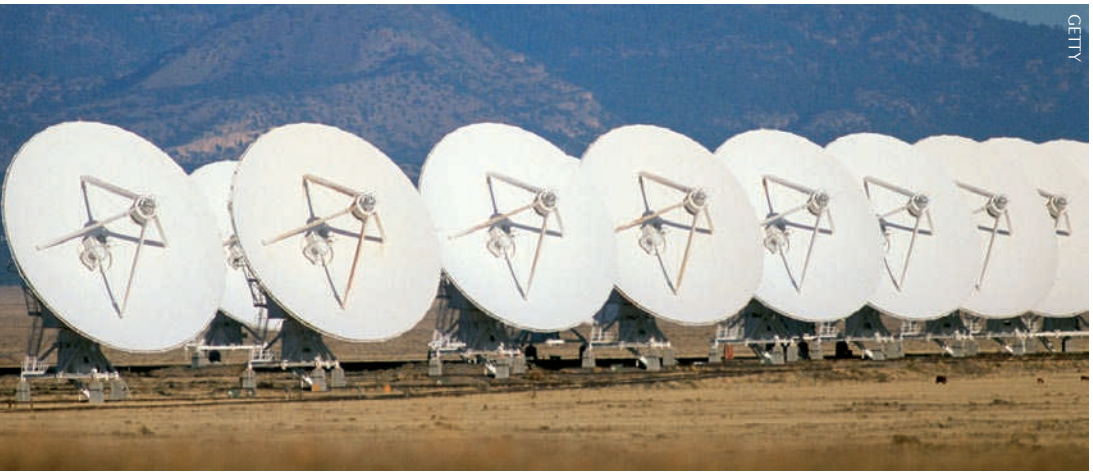
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ORIGINAL RESEARCH PAPER Giorgetti, L. *et al.* Noncooperative interactions between transcription factors and clustered DNA binding sites enable graded transcriptional responses to environmental inputs. *Mol. Cell* **37**, 418–428 (2010)
FURTHER READING Segal, E. & Widom, J. From DNA sequence to transcriptional behaviour: a quantitative approach. *Nature Rev. Genet.* **10**, 443–456 (2009)