GENE EXPRESSION

A singular level of noise

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Cells as a whole make a lot of noise — made up of fluctuations in protein levels — but understanding where noise comes from means breaking it down into its individual components and investigating the sounds made by a single cell. Two studies have now measured how protein abundance, and therefore noise, varies across individual yeast cells, and link it to the molecular processes behind our cellular cacophony.

Bulk analyses of DNA expression are informative about how gene expression varies, but they do not get to the bottom of the issue: what molecular phenomena cause noise in a single cell, and how does noise respond to environmental influences? In the first study, John Newman and colleagues applied flow cytometry, which can quantify the protein concentration in individual cells, to over 4,000 strains of *Saccharomyces cerevisiae* in which each gene was tagged with GFP at the endogenous genomic locus. This combined technique

was then applied to create a protein abundance profile of cells grown in minimal and rich media.

Two significant patterns emerged. First, there is an inversely proportional relationship between noise and protein levels, suggesting that variation in protein expression is governed mainly by the low numbers of many mRNA molecules. Second, there is a qualitative difference in the way in which functional classes of protein are affected by noise: heat-shock proteins and those involved in the stress response are noisier than those required for translation, for example. This pattern might make evolutionary sense — proteins involved in core biochemical processes (such as protein production and destruction) might be encoded by quiet genes, whereas those that enable cells to respond to environmental conditions might be encoded by noisy genes, allowing a population of cells to ensure that it always has some individuals that are prepared to survive environmental changes.

In the second study, Arren Bar-Even and colleagues used a similar combined approach to measure the variation in abundance of 43 fluorescently labelled proteins that were expressed under 11 environ-

mental conditions. Their conclusions — again gleaned from studying single budding-yeast cells — agree with those reported above: there is an inverse relationship between protein levels and the amount of noise, which in turn is caused by the random birth and death of individual mRNA molecules or the stochastic activation of promoters. Importantly, this relationship holds across the different growth conditions and across all time points, and was corroborated by sophisticated mathematical modelling.

The strength of these two studies lies in studying a large number of genes and recording natural protein fluctuations in single cells rapidly, accurately and at high sensitivity. These results describe the situation for most proteins, although a more complete picture of how noise is generated will come from pursuing those proteins that, because of the involvement of other regulatory mechanisms, fall outside this trend.

Tanita Casci

ORIGINAL RESEARCH PAPERS Newman, J. R. S. *et al.* Single-cell proteomic analysis of *S. cerevisiae* reveals the architecture of biological noise. *Nature* 14 May 2006 (doi:10.1038/nature04785) | Bar-Even, A. *et al.* Noise in protein expression scales with natural protein abundance. *Nature Genet.* 21 May 2006 (doi:10.1038/ng1807)

FURTHER READING Kaern, M. *et al.* Stochasticity in gene expression: from theories to phenotypes. *Nature Rev. Genet.* 6, 451–464 (2005)