*Nature Reviews Molecular Cell Biology* | AOP, published online 15 november 2008; doi:10.1038/nrm2535

GENE EXPRESSION

# Coming in waves

> …cells use a more dynamic mechanism to regulate target genes.

Cells respond rapidly to extracellular signals by regulating the expression of target genes. This is achieved by modifying transcription factors that translocate to the nucleus and activate the expression of many downstream genes. Biochemistry and imaging of fixed cells have shown that transcription factors translocate to the nucleus in a graded fashion. Using time-lapse microscopy of live individual cells, Elowitz and colleagues now show that cells use a more dynamic mechanism to regulate target genes.

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To investigate how signals are encoded dynamically in transcription factor activities and how protein coordination is achieved in individual cells, the authors examined the calcium stress response pathway in *Saccharomyces cerevisiae*. In yeast, cellular responses to extracellular calcium are mediated by Crz1, the calcineurin-responsive zinc-finger transcription factor. The activity of Crz1 is modulated by phosphorylation and dephosphorylation; on addition of calcium, Crz1 becomes dephosphorylated and translocates to the nucleus.

To understand how Crz1 phosphorylation dynamics respond to calcium and regulate the more than 100 different targets that are necessary for calcium adaptation, Elowitz and colleagues used time-lapse microscopy of green fluorescent protein (GFP)–Crz1 localization dynamics. Upon addition of calcium, individual cells showed a rapid, synchronized burst of Crz1 nuclear localization. This initial burst was followed by sporadic unsynchronized localization bursts (typically lasting 2 minutes). The frequency — but not the duration or amplitude — of these bursts positively correlated with calcium concentration**.** Thus, cells use frequency modulation in their regulation of transcription factor activities.

What functionality does this frequency-regulated modulation of Crz1 localization bursts provide for the regulation of downstream genes? Based on computer modelling, the authors show that the frequency-modulation regulation of bursts allows transcription factors to modulate the expression of multiple target genes in concert, across a wide, dynamic range of expression levels and independent of promoter characteristics; this theory was experimentally confirmed with natural and synthetic Crz1-target promoters.

To investigate the generality of the localization bursts, the authors examined another yeast protein, the stress-response transcription factor Msn2. They show that Msn2 exhibits similar, but largely uncorrelated, localization bursts under calcium stress. The authors anticipate that frequency-modulated regulation of localization bursts might represent a general principle by which cells coordinate multigene responses to external signals.

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**ORIGINAL RESEARCH PAPER** Cai, L. *et al.* Frequency-modulated nuclear localization bursts coordinate gene regulation. *Nature* **455**, 485–490 (2008)



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