ABSTRACT

Genetically identical cells harvested in the same environment exhibit heterogeneity in gene expression. This phenomenon, termed gene expression noise, has been measured in several model organisms under various conditions. However, we still do not have a clear understanding of (1) the factors responsible for generating gene expression noise, or (2) the potential consequences noise can have on cellular processes. In an attempt to investigate these issues, we have determined the effects of 1) directional selection, 2) promoter mutation and 3) fluctuations in transcription factor localization on gene expression noise. First, we have used analytic and computational modeling of the effects of directional selection on gene expression noise to discover that, assuming expression can be described by up to two independent parameters, μ, mean, and σ, noise, strong directional selection yields an increase in noise. Next, we generated mutant promoter libraries and measured gene expression to determine the effects of *cis*-regulatory mutations on gene expression noise. Here we found that the expression noise can indeed be modulated by mutation independent of mean expression levels, lending credence to the previously mentioned analytical result. Based on this result, that mutations can harness noise, we wanted to determine whether the binding and unbinding of transcription factors to promoter regions also contributed to gene expression noise. To do so, we analyzed the localization dynamics of a transcription factor Crz1. We determined that Crz1 translocates to the nucleus in coherent bursts of localization in response to calcium. The frequency, but not the duration, of these bursts increases with the concentration of extracellular calcium. This frequency modulation propagates downstream of Crz1, enabling proportional regulation of target genes. Intrigued by this result, we characterized different types of localization dynamics used by the yeast proteome. We have found several classes of localization behavior, including proteins that burst on several timescales, exhibit static heterogeneity, and show amplitude modulation. Strikingly, several of these dynamic localization systems must co-exist in the same cell under the same conditions. Amongst the proteins that burst on a fast timescale like Crz1, Msn2 and Mig1 are transcription factors that both burst when deprived of glucose. Furthermore, both regulate a common set of target genes. Interestingly, when imaged together, the proteins exhibit correlations on two timescales, a positive correlation

that typically lasts for an hour and an anti-correlation that lasts a few minutes. We are continuing to investigate the potential regulatory impact of these correlations by measuring the expression of their combinatorial target genes.