mRNA noise reveals that activator regulation of transcriptional bursts is biphasic

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***Short Abstract* — Transcriptional regulation requires fast and accurate transfer of a signal. However, transcription of regulated genes occurs in bursts that generate variability in expression. This noise affects signal transmission and can even change cellular phenotype, depending on the kinetics of transcription. Here, we ask how *cis* and *trans* factors affect the kinetic parameters of regulated transcription, burst frequency and burst size. We infer bursting parameters from mRNA distributions measured with mRNA FISH at the synthetic tetO and natural *PHO* promoters in *S. cerevisiae*. We measure that increasing activator levels first increase burst size and then burst frequency, creating a biphasic response that may be common to many regulated genes.**

***Keywords* — transcriptional bursting; stochastic gene expression; transcriptional regulation; bimodality.**

I. Background

GENE expression is a stochastic process that can result in cell behavior that is qualitatively different to a deterministic system [1]. Single molecule experiments have established that noise in gene expression is often due to transcriptional bursting [2], especially at highly regulable genes. A simple model where genes are inactive for exponentially distributed times punctuated by geometric bursts of mRNA production can describe these dynamics [3]. Transcriptional output can therefore be regulated via burst frequency and/or burst size [3,4] and these parameters can be inferred from the steady-state distribution of transcripts per cell in a population [4,5]. Bursting parameters can affect cell behavior but it is less understood how they are regulated within the cell.

II. Results

A. Regulatory mode affects the stability of bimodality from positive feedback

It is well-established that stochastic transcription can qualitatively affect expression. For example, theory [6] and experiment [7] have demonstrated that noise can create bimodality in positive feedback without deterministic bistability. However, we show that this is only true when activators regulate burst frequency. In contrast, activator regulation of burst size destabilizes deterministic bistability in positive feedback. Therefore the kinetics of regulation are important in controlling cell behavior.

B. Two regulated promoters are activated by first increasing the size and then the frequency of bursts

To determine how transcriptional activators increase gene expression, we deduce bursting kinetics from steady-state mRNA distributions measured in individual yeast cells using single molecule mRNA FISH. We find that a synthetic tetO and natural *PHO5* promoter turn on through activators first increasing burst size, then burst frequency. This biphasic response is in contrast to previous work suggesting that activators predominately regulate burst frequency [7,8], likely due to measurement techniques. We hypothesize that this strategy minimizes noise within regulated genes' requirement for a large dynamic range. We comment on the extent to which the measured mRNA fluctuations originate from transcriptional bursting versus extrinsic sources.

III. Conclusions

The regulable parameters of transcription are burst size and burst frequency. The extent to which each is regulated potentially affects cell phenotype. We observe gene activation via regulation of burst size and then burst frequency. It will be interesting to see if this biphasic response is common to most regulated genes.

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