Abstract Submitted
for the MAR12 Meeting of
The American Physical Society

mRNA Noise Reveals that Activators Induce a Biphasic Response in the Promoter Kinetics of Highly Regulated Genes KATIE QUINN, Massachusetts Institute of Technology, TSZ-LEUNG TO, University of California, San Francisco, NARENDRA MAHESHRI, Massachusetts Institute of Technology — A dominant source of fluctuations in gene expression is thought to be the process of transcription. The statistics of these fluctuations arise from the kinetics of transcription. Multiple studies suggest the bulk of fluctuations can be understood by a simple process where genes are inactive for exponentially distributed times punctuated by geometric bursts of mRNA. Yet it's largely unknown how cis and trans factors affect the two lumped kinetic parameters, burst size and burst frequency, that describe this process. Importantly, how these parameters are regulated in a single gene can qualitatively affect the dynamical behavior of the network it is embedded within. Here, we ask whether transcriptional activators increase gene expression by increasing the burst size or burst frequency. We do so by deducing these parameters from steady-state mRNA distributions measured in individual yeast cells using single molecule mRNA FISH. We find that for both a synthetic and natural promoter, activators appear to first increase burst size, then burst frequency. We suggest this biphasic response may be common to all highly regulated genes and was previously unappreciated because of measurement techniques. Furthermore, its origins appear to relate to cis events at the promoter, and may arise from combinations of basal and activator-dependent bursts. Our measurements shed new light on transcriptional mechanisms and should assist in building synthetic promoters with tunable statistics.

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Date submitted: 20 Nov 2011 Electronic form version 1.4