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Calibrating stochastic models of transcriptional bursting in single mammalian cells

In both prokaryotes and eukaryotes, stochasticity in the dynamics of mRNA and protein expression has important consequences on gene regulation and on non-genetic cell-to-cell variability. Here, we show how discontinuous transcription of mammalian genes leads to broad spectra of temporal bursting in mRNA synthesis. To monitor transcription at high temporal resolution, we designed chromosomally-integrated vectors encoding a very short-lived luciferase in combination with ultra-sensitive bioluminescence microscopy. These data enabled us to develop and calibrate a probabilistic model of gene expression to estimate gene-specific transcription burst sizes and switching rates. The model was further used to deconvolve the time traces, which showed that rapid bursting at timescales of tens of minutes may be an intrinsic property of transcription in mammalian cells, and lead to the characterization of refractory periods of variable duration in the inactive state. Experiments in which the regulatory elements were modified showed that the bursting kinetics was markedly altered by sequence modifications of cis-regulatory sequences. This high temporal resolution monitoring of transcription is readily applicable to many systems; including the circadian oscillator in which we show that increased bursting frequency precede maximal burst sizes by few hours.