Enhancer-Promoter Contacts Influence Transcriptional Kinetics

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Background

Transcription Occurs in Discrete Bursts

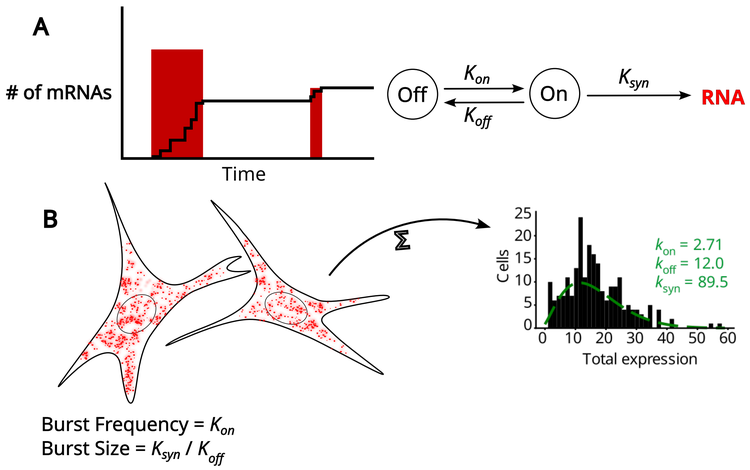

Figure 1. At most genes, transcription happens in short bursts followed by longer periods of senescence. **(A)** Illustration of a two-state model of expression found suitable for most promoters. **(B)** Schematic of RNA count beta-poisson distribution derived from smFISH. Kinetic parameters can be inferred using maximum profile-likelihood from Larsson et al. (2021). ***Burst frequency*** is described as the rate of initiation of bursts (min^{-1}) whereas ***burst size*** is the number of mRNAs per given burst.

1. Enhancers Modulate Burst Frequency

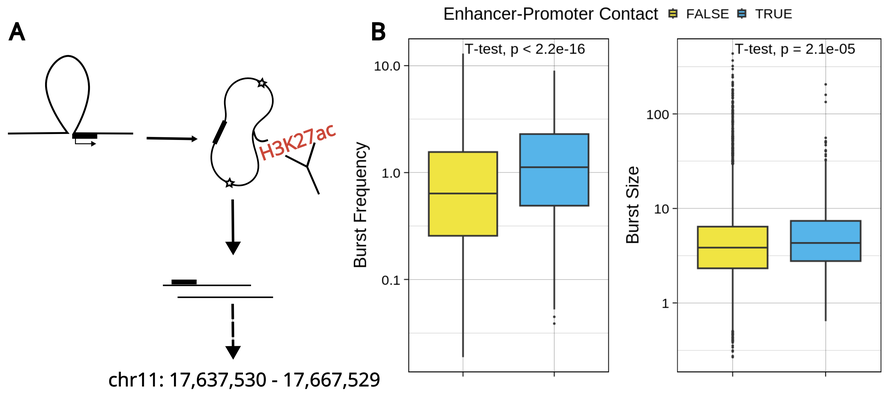

Figure 2. H3K27ac HiChIP data reveals enhancer-promoter (EPs) contacts positively influences burst frequency and to a lesser degree, burst size. **(A)** HiChIP is a chromatin capture technique used to identify interacting sites enriched with a particular mark or DNA binding protein. H3K27ac is a common enhancer and promoter histone mark and can be used to identify linkages between both. **(B)** HiChIP data in mouse embryonic fibroblasts (MEFs) from Yang et al. (2022) (GSE193079) and processed whole genome transcriptional kinetics data from Larsson et al. (2021) show that promoters, when in contact with one or more enhancers have a greater burst frequency and burst size.

Results

2. Multiple Enhancer-Promoter Contacts Influence Kinetics

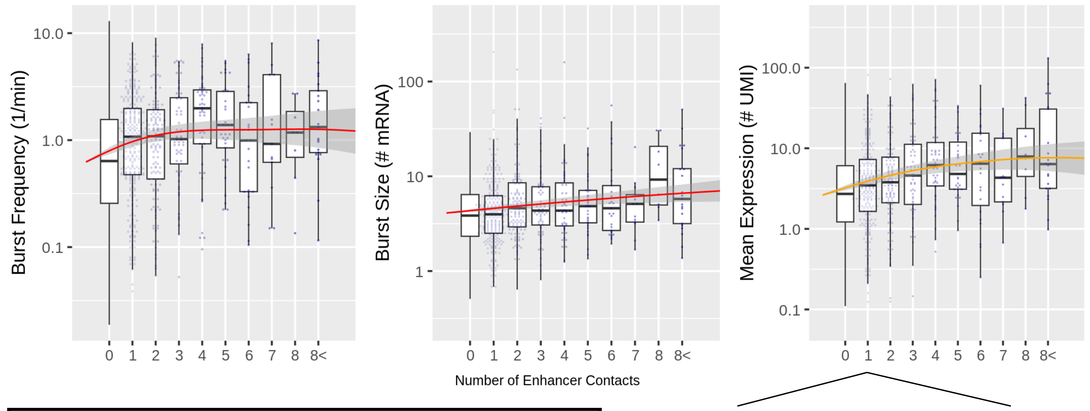

Figure 3. Transcriptional kinetic parameters scale differently with increasing enhancer-promoter contacts. Processed kinetics data from Larsson et al. (2021). Smooth curves are generated from loess regression on the whole distribution. Burst frequency appears asymptotic at 2-3 enhancers acting at the same promoter. Burst size increases linearly with increasing enhancer contacts (β = 1.052, $p < 0.0001$) .

3. Topologically Associated Domain Boundaries are Kinetically Invariant

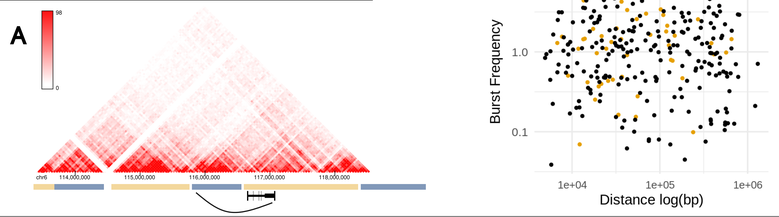

Figure 4. The presence of topologically associated domain (TAD) boundaries does not alter the kinetics for single EP linkages. **(A)**. Example of an EP crossing an TAD boundary. MEF TAD annotations are derived from HI-C from Li et al. (2022). **(B)** Burst Frequency of single linked EPs versus genomic distance between enhancer and promoter. Using a multiple linear model neither coefficient was significant ($p > 0.4$). A similar result was found when modeling burst size.

4. Enhancer-Promoter Contacts Lowers Intrinsic Noise

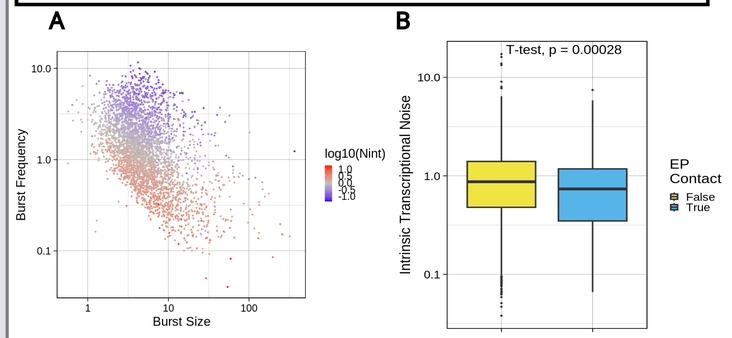

Figure 5. EP contacts influence cell-to-cell variation. **(A)** Kinetic parameters and their relationship to noise estimates from raw scRNA-seq data from Larsson et al. (2021). There exists a strong negative relationship between burst frequency and transcriptional noise (R^2 = -0.91, $p < 0.001$) and a slight positive relationship with burst size (R^2 = 0.11, $p < 0.001$). **(B)** The presence of an EP contact lowers intrinsic transcriptional noise derived from allele specific UMI count variation.

5. Super-Enhancers Increases Burst Frequency

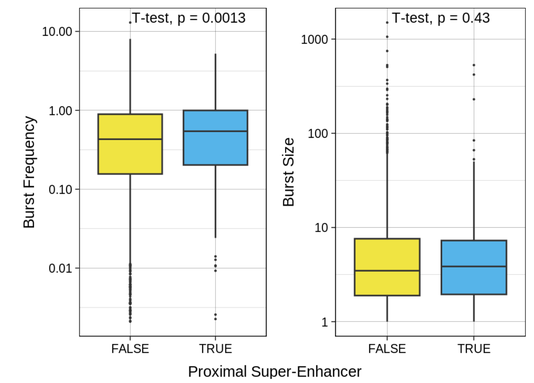

Figure 6. Super-Enhancers (SEs) increases burst frequency in isolation of burst size. Med1 Enriched, stitched enhancer regions induce greater burst frequencies in proximal genes (<12kb) in mESCs. Constiuent enhancers derived from intersected peaks of Nanog, Sox2 and Oct4 from Whyte et al. (2013). SEs were called using the ROSE algorithm on Med1 read density.

References

Larsson, A. J. M. et al. Transcriptional bursts explain autosomal random monoallelic expression and affect allelic imbalance. PLOS Computational Biology 17, e1008772 (2021).

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Key Takeaways

- **Kinetics data suggests enhancers have a dual role in transcription: initiating a burst of transcription and maintaining the production of mRNAs.**
- **Multiple enhancers may operate redundantly when initiating, but additively when maintaining transcription.**
- **Cell-to-cell variation at individual genes from intrinsic sources is a product of bursting which concordantly decreases in the presence of an EP.**