The kinetic structure of silent transcription intervals underlying transcriptional bursting in single mammalian gene promoters

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***Short Abstract* — In mammals, most genes appear to be transcribed during short periods called transcriptional bursts, interspersed by silent intervals. Based on stochastic modeling of time lapse bioluminescence traces in single cells, we infer a minimal model accounting for the recently observed refractory period between successive transcriptional events and characterize the kinetics of the underlying processes in different mammalian promoters.**

***Keywords* — Noise in gene expression, transcription mechanisms in mammals, kinetics measurement in single cells**

I. Purpose

GENE transcription in mammals is known to occur mainly during short and intense periods referred as to transcriptional bursts, interspersed by silent periods. The nature of these silent periods has been hypothesized to reflect the accumulation of stable changes in the chromatin template mediating the sequential assembly of the transcription machinery [1], but the number of rate limiting steps required before activation of the gene and their typical timescales remain unknown. In order to estimate these characteristics *in vivo*, we further extend a probabilistic framework to model single cell time lapse recording based on a stochastic gene expression model that describes the basic processes of gene activation, transcription, translation, and degradation of mRNA and proteins [2].

II. Methods

Motivated by the recent finding of a refractory period between successive gene activation events in mammals [2,3], we propose an extension of the telegraph model [4] accounting for unimodal waiting time distribution, where the gene activity is modeled by one active state and multiple sequential inactive states describing the promoter progression toward activation. The number of inactive states defines a class of nested models which enable computation of a likelihood for the measured reporter bioluminescence time traces. We select the optimal model and estimate the unknown transition rates using Reversible Jump Markov-Chain Monte Carlo (MCMC) sampling [5].

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III. Results

Applying our inference framework on single cell time-lapse measurements of short-lived luciferase reporter expression controlled by endogenous, circadian, or artificial promoters in mouse fibroblasts, we demonstrate that several inactive steps (five on average) are required to model the waiting time of the promoters and the average time of those steps is in the range of 30 min. Moreover, we observe substantial variability on the number of inactive states and their duration. Synthetic promoters with a simple architecture displayed a smaller number of states on average than endogenous ones.

We also study the implications of those inactive states on the noise characteristics of each promoter, using the analytical noise expression derived by Zhang et al. [6]. We identify two different strategies leading to transcriptional noise reduction among the analyzed promoters, either higher mRNA expression or larger number of inactive states leading to a more regular activation pattern.

IV. Conclusion

We presented a minimal extension of the telegraph model which accounts for the refractory period and were able to estimate the kinetic parameters and the number of inactive states applying MCMC sampling. Most genes required several inactive steps to model the waiting time of the promoters and they show two different strategies leading to mRNA noise reduction: high expression or many inactives states.

References

[1] Hager GL, Elbi C, Johnson TA, Voss T, Nagaich AK, Schiltz RL, Qiu Y, and John S (2006). Chromatin dynamics and the evolution of alternate promoter states. *Chromosome Research*, 14(1):107-116.

[2] Suter DM, Molina N, Gatfield D, Schneider K, Schibler U, and Naef F (2011). Mammalian Genes Are Transcribed with Widely Different Bursting Kinetics. *Science*, 332(6028):472-474.

[3] Harper CV, et al. (2011). Dynamic Analysis of Stochastic Transcription Cycles. *PLoS Biology*, 9(4):e1000607.

[4] Peccoud J, and Ycart B (1995). Markovian modeling of gene-product synthesis. *Theoretical Population Biology*, 48(2):222-234.

[5] Green PJ (1995). Reversible jump Markov chain Monte Carlo computation and Bayesian model determination. *Biometrika,* 82(4): 711-732

[6] Zhang J, Chen L, and Zhou T (2012). Analytical Distribution and Tunability of Noise in a Model of Promoter Progress. *Biophysj*, 102(6):1247-1257