Effects of Network Topology on the Reliability of Transcriptional Regulation

Alistair N. Boettiger[1], Peter L. Ralph[2,3], Steven N. Evans[3,4]

***Short Abstract* — Gene expression is controlled by a complex network of interacting macromolecules, some of which are present in very low copy number per cell. Its precision and reliability of expression can be affected considerably by molecular 'noise' arising from diffusion-mediated interactions of low copy number factors, and the degree to which this happens depends on the topology of the network of interactions. Here we present a mathematical approach to explore how interaction topology affects the molecular noise in a biochemical network. We apply this method to explain two recently reported properties of 'paused' genes.**

***Keywords* — Gene expression, stochastic modeling, paused polymerase.**

I. Purpose

RECENT investigations in metazoan transcription have revealed a highly diverse array of regulatory strategies in eukaryotes. It is largely believed that initiation of transcriptional machinery assembly at the promoter is the primary mechanism for modulating the expression of genes [1], as indicated by prior studies in yeast [2, 3]. However, whole-genome assays for polymerase binding have demonstrated that metazoans, from *Drosophila* to humans, have assembled transcriptional machinery loaded on the promoters of 5-30% of non-expressed genes (so-called "stalled" or "paused" polymerase), thus indicating an alternative mechanism in which transcript elongation is the controlled step [4,5,6].

The selective pressures, which have lead to this rearragement of the topology of regulation, from controlling initiation to controlling elongation, comprise a very active field of research. Recent reports have shown that these 'paused' genes are activated in a faster [7] and more synchronous fashion than other initiation regulated genes [8]. The theoretical connection between speed, synchrony and topology, however, has not been explored.

II. Methods

We develop a mathematical toolbox to allow for the analysis of the stochastic properties of macromolecular assembly chains. The specific properties we examine are speed of assembly, variation in time to assembly (i.e. synchrony of independent processes), and variation in the number of catalyzed events (e.g. the number of mRNA synthesized). We use continuous time Markov chains to describe the assembly processes. We illustrate how a complex chain can be decomposed into different subchains to ensure that the computations are still analytically tractable. Our approach avoids the need for computationally expensive simulations, like the Gillespie algorithm commonly used to study these processes. It also provides direct, symbolic solutions for how the properties of interest mentioned above depend on the individual reaction rates. General-purpose code implementing these tools is provided.

III. Conclusion

With this method we provide a theoretical demonstration that the topology elongation regulation itself should be expected to improve initiation speed and synchrony compared to initiation regulation of the same promoter. Additional changes in the promoter strength etc are not required. We make new predictions about the effect of pausing on the reliable control of transcript number. We also identify which elements in the transcription induction pathway are most sensitive to molecular noise and thus may be most evolutionarily constrained.

Acknowledgements: ANB is supported by the NSF GRFP.

[1]Biophysics Graduate Group and Department of Molecular and Cellular Biology, University of California, Berkeley CA alistair@berkeley.edu
[2]Department of Evolution and Ecology, University of California, Davis
[3]Department of Statistics, University of California, Berkeley
[4]Department of Mathematics, University of California, Berkeley

References

[1] Juven-Gershon, T., et al., *The RNA polymerase II core promoter -- the gateway to transcription.* Current opinion in Cell Biology, 2008. **20**: p. 253-259..

[2] Keaveney, M. and K. Struhl, *Activator-Mediated Recruitment of the RNA Polymerase II Machinery Is the Predominant Mechanism for Transcriptional Activation in Yeast.* Molecular Cell, 1998. **1**(6): p. 917-924.

[3] Ptashne, M. and A. Gann, *Transcriptional activation by recruitment.* Nature, 1997. **386**: p. 569-577.

[4] Core, L.J., J.J. Waterfall, and J.T. Lis, *Nascent RNA Sequencing Reveals Widespread Pausing and Divergent Initiation at Human Promoters.* Science, 2008. **322**(19): p. 1845-1848.

[5] Guenther, M.G., et al., *A Chormatin Landmark and Transcription Initiation at Most Promoters in Human Cells.* Cell, 2007. **130**: p. 77-88

[6] Zeitlinger, J., et al., *RNA polymerase stalling at developmental control genes in the Drosophila melanogaster embryo.* Nature Genetics, 2007. **39**(12): p. 1512-1516.

[7] Yao, J., et al., *Intranuclear Distribution and Local Dynamics of RNA Polymerase II during Transcription Activation.* Molecular Cell, 2007. **28**: p. 978-990.

[8] Boettiger, A.N. and M. Levine, *Synchronous and stochastic patterns of gene activation in the Drosophila embryo.* Science, 2009. **325**: p. 471-473.