Making the right 'noise': bimodality, power-laws and transcriptional pulsing

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When mRNA synthesis is controlled by transcriptional-pulsing, i.e. the gene switches stochastically between an active state in which there is transcription and an inactive state, mRNA distributions with long tails are found. Using a stochastic, Master Equation treatment, we present the exact, analytic, time-dependent distribution of the mRNA number [1]. We show existence of bimodal distributions that evolve into distributions with power-law behavior as reaction rates are varied over biologically relevant scales. The time-evolution of these distributions is presented. The relevance of our results to experiments and an alternate, useful representation of the mRNA distribution as a superposition of Poisson distributions are also presented.

***Keywords* — transcriptional pulsing, stochastic model, mRNA distributions, bimodal distributions, Random telegraph signals, mixed Poisson distributions**

I. Experimental Motivation

Cell to cell variability is now recognized as a major aspect of cellular response to stimuli, a variability which is hidden in cell population studies. The most egregious example is provided in cases where a graded average response hides the all-or-nothing behavior of single cells [2, 3, 4].

Recent experimental studies of mRNA distributions have shown strong evidence for transcriptional noise beyond what can be described by a simple Poisson process; in particular, transcriptional pulsing has been observed in both prokaryotes and eukaryotes. Raser and O'Shea [5] studied intrinsic and extrinsic noise and showed that the noise associated with a particular promoter could be explained in a transcriptional pulsing model. Transcriptional bursts were also recorded in E. Coli [6] by following mRNA production in time, and their statistics computed. Evidence for the pulsing model of transcription, obtained from fluorescent microscopy, has as well been presented in Dictyostelium Discoideum [7]. Transcriptional bursts have also been detected in Chinese hamster ovary cells [8]. Thus in these experiments production of mRNA occurs in a sequence of bursts of transcriptional activity separated by quiescent periods. Transcriptional bursting, an intrinsically random phenomenon, thus becomes an important element to consider when evaluating cell to cell variability. One can predict that in many cases it will be a significant part of the overall noise, and most certainly of intrinsic noise.

II. Theoretical Results

We provide a comprehensive theoretical analysis of the transcriptional pulsing model with an exact solution to the time-dependent Master Equation for mRNA production within a stochastic model [1]. We find that the system exhibits a surprising variety of distributions of mRNA number: this includes a bimodal distribution with power-law behavior between the peaks that evolves into a scale-invariant power-law distribution over a range of mRNA number as we vary the rates of activation and inactivation. We discuss how these steady state distributions are reached as a function of time. We find that the mRNA lifetime is a key parameter in identifying the different regimes. To explore implications these behaviors for the protein encoded by the mRNA, we have performed numerical simulations of a simple model using the Gillespie algorithm in which proteins are produced in a birth-death process: when the protein decay rates are much larger than the mRNA decay rate the protein distributions reflect the mRNA distributions; when the protein decays more slowly the protein distribution can be very different from that of the parent mRNA. We thus provide an overview of possible behaviors which - within the confines of the model considered - yield a framework for understanding experimental results on transcriptional bursting across prokaryotes and eukaryotes.

References

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