Stochastic Modeling of mRNA Bursts: The Example of ER-mediated Transcription

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***Short Abstract* —Questions related to the dynamics of initiation and regulation of gene transcription in eukaryotes are still in dispute. We review the existing biological models and solve equations describing relevant stochastic models. We relate the solutions to our recent experimental evidence concerning the estrogen receptor (ER)-mediated transcription.**

I. Introduction

IT has been recently determined utilizing fluorescence recovery after photobleaching (FRAP) that there may exists a pronounced "fast" (order of 5-10 sec.) stochastic component of transcription [1]. Also, Raj et al. [2] observed stochastic bursts of transcription from a reporter gene inserted into the genome of Chinese Hamster Ovary (CHO) cells, with either 1 or 7 DNA binding sites for the transcription factor of a single gene copy. Raj et al. [2] built a mathematical model in which they assumed that the transitions from the inactive (I) to the active (A) state are random and occur with intensities λ and γ, and estimated the expected times the reporter gene was transcriptionally active and inactive. Stochastic effects are present even a large number of arrayed promoter sites interact with a large number of bound molecules. In [3], in a cell line containing total of 800-1200 binding sites in 200 tandemly arrayed gene copies, a pronounced cell-to-cell variability was observed in RNA FISH signal and GR-MMTV. Voss et al. [3] hypothesize that the GR receptors exist in a *variety of multi-protein complexes*, which are *stochastically recruited to response elements* and remain *associated for brief times*.

II. Experimental System

We developed biological PRL-HeLa system containing a multicopy locus of the prolactin gene and allowing direct visualization of GFP-estrogen receptors (GFP-ER) in living or fixed cells, and quantification of transcription by visualizing reporter gene mRNA [1]. Time course FISH studies reveal the amount of cycling of mRNA accumulation while array size remains constant. Experimental approaches such as high-throughput microscopy assess the stochasticity in the regulation of the reporter gene. For example the amount of gene mRNA is correlated to the quantitative measurement of GFP-ER and coactivator(s) over time, during agonist/antagonist treatments (e.g., estradiol vs. tamoxifen), which leads to measure the sources of intrinsic and extrinsic fluctuation in transcription.

III. Stochastic Modeling and Voss et al. Hypothesis

Our objective is a mathematical model to clarify the dynamic, cooperative, and cyclic nature of gene expression, describing cell to cell diversity and transcriptional bursts. Work in our group includes stochastic models [4] such as e.g., a system of N serially arrayed genes, each with K functional binding sites in the promoter region. Partial list of possibilities includes: (i) Deterministic approximation, K and/or N large, and/or λ and γ and μ large. (ii) Stochastic effects due to small numbers of binding sites, K and N small. (iii) Stochastic effects due to limiting co-factors and/or low abundance of transcription factors, λ small. For example, the model in Raj et al. [2] has $N = 1$, $K = 1$ or 7, and μ large in one of the versions. The models in Hat et al. [5] involve $N = 1$, 2, or 4 and $K = 1$ with large μ.

We provide analytic exact and asymptotic solutions of the time-continuous Markov processes describing the variants reported in the literature and apply these solutions to data on variability of mRNA level in the PRL-HeLa system. In this way, we supply mathematical justification for the Voss et al. [3] theory of stochastic interactions in transcription.

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