The role of time scales in extrinsic noise propagation

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***Short Abstract* — Cell-to-cell variability in the number of proteins has been studied extensively experimentally. There are many sources of this stochastic variability or noise that can be classified as intrinsic, due to the stochasticity of chemical reactions and extrinsic, due to environmental differences. The different stages in the production of proteins in response to a stimulus, the signaling cascade before transcription, transcription, and translation are characterized by different time scales. We analyze how these time scales determine the effect of the reactions at each stage on different sources of noise.**

***Keywords* — extrinsic noise, intrinsic noise, protein variance, mRNA variance, stochastic gene expression**

I. BACKGROUND

Chemical reactions are inherently probabilistic and in the context of gene expression, since the numbers of key biochemical molecules (genes, mRNAs) involved are small, even if genetically identical cells in identical fixed environments are considered, the resultant cell to cell variability in protein numbers may well be comparable to their mean numbers[1]. Thus `intrinsic stochasticity' in protein numbers needs to be considered in understanding how gene regulation is implemented by proteins in the face of such noise and has been the subject of several experimental and theoretical studies.

There is mounting evidence though, that in both prokaryotes and eukaryotes a significant component of the noise in protein numbers is typically `extrinsic', i.e., resulting from variability in the environments presented to the transcriptional and translation machinery in each cell [1-5]. The pioneering work of Elowitz et-al [2] has made it possible to quantify the intrinsic and extrinsic components of noise in a given system. They provided an experimental construction that can directly measure these two components of the total noise for a given protein.

II. RESULTS

The different stages in the production of proteins in response to a stimulus, the signaling cascade before transcription, transcription, and translation are characterized by different time scales. Using the definitions of Elowitz et-al [2], we analyze how these time scales determine the effect of the reactions at each stage on intrinsic and extrinsic components of noise.

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For example, even if intrinsic noise dominates the fluctuations in mRNA number, for typical mRNA and protein lifetimes we find that extrinsic noise can dominate corresponding protein number fluctuations. Such results are important in determining the importance of intrinsic noise at earlier stages of a genetic network on the products of subsequent stages.

There is experimental evidence to show that some sources of extrinsic variability themselves undergo stochastic dynamics [5, 7-9]. Also, extrinsic noise is commonly assumed to affect transcription and/or translation rate/s [1,4,7]. We provide a theoretical framework in which such dynamical sources of extrinsic noise can be studied. Using this framework we derive exact results for the propagation of dynamic extrinsic noise in the transcription rate from the messenger-RNA to the protein stage. Since such extrinsic noise is both dynamic and multiplicative, the model is non-linear. The inadequacy of traditional frameworks, like that of Linear Noise Approximation, in explaining numerically observed trends for such a model has been previously remarked upon [7]. We also compare our exact, analytical results to the numerical studies performed by Swain et-al [7]. We use our results to show that when the dynamical extrinsic noise is auto-correlated on time-scales comparable to the cell-cycle time, i.e., to typical protein lifetimes, as observed in the experiments of Rosenfeld et-al [5], the scaling of the total noise in protein numbers scales with the inverse square root of mean protein numbers[6] still continues to hold to a very good approximation. We have derived our results exactly, analytically, even though the model is nonlinear and includes multiplicative dynamic extrinsic noise, by further developing the framework of the Poisson Representation for gene regulation models, provided in one of our other works.

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