Stochastic modeling of post-transcriptional regulation of gene expression by non-coding RNAs

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Short Abstract **— We study the canonical model of stochastic gene expression wherein non-coding small RNAs (sRNAs) and mRNAs interact with each other leading to stoichiometric mutual degradation. Due to the presence of the nonlinear interaction term between sRNAs and mRNAs, the exact solution of the model is analytically intractable and theoretical analysis typically involves mean-field approaches. However, mean-field results are inaccurate in the limit of strong interactions and low abundances; thus alternative theoretical approaches are needed. In this work, we obtain analytical results for the canonical model of regulation of stochastic gene expression by sRNAs in the strong interaction limit. We derive analytical results for the steady-state generating function of the joint distribution of mRNAs and sRNAs in the limit of strong interactions and use the results derived to obtain analytical expressions characterizing the corresponding protein steady-state distribution. Furthermore, under simplifying assumptions, we also derive the large deviation rate function characterizing rare events associated with the rate of protein production.**

Keywords — **Stochastic gene expression, Post-transcriptional regulation, Non-coding small RNAs, Rare events.**

I. INTRODUCTION

Intrinsic randomness in gene expression process can play an important role in stochastic cell fate decisions [1-2]. Cellular control of such intrinsic randomness (noise) depends on the regulation of gene expression which occurs at various stages. While considerable research has focused on regulation of gene expression by transcription factors, there has been growing interest in understanding gene regulation at the post-transcriptional level by non-coding sRNAs (sRNAs). Non-coding sRNAs are known to play key roles in regulating diverse cellular processes [3-4] and dysregulation of and by sRNAs is linked to various diseases including cancer [5]. Correspondingly, there is significant interest in quantitatively modeling the effect of post-transcriptional regulation on fluctuations [6] and rare events

in gene expression [7].

In the present work, we focus on quantitative understanding of gene regulation due to these sRNAs. For this, we use the canonical model [8] of stochastic gene expression that incorporates post-transcriptional regulation. In this model both sRNAs and mRNAs interact with each other leading to stoichiometric mutual degradation. The presence of nonlinearity due to this interaction makes the model analytically intractable. However, in the limiting case of strong interactions, we have derived analytical results for this model.

II. RESULTS

For the canonical model studied in this work, we derive analytical results for the steady-state joint distribution of mRNAs and sRNAs in the limit of strong interactions. The results derived at the level of mRNAs are then extended to derive analytical expressions for the corresponding protein distribution. Characterization of protein probability distribution in this limit is an important step in quantifying post-transcriptional regulation of noise in gene expression. Furthermore, within the framework of canonical model and under biologically relevant simplifying assumptions, we also derive the large deviation rate function characterizing rare events in the rate of protein production.

III. CONCLUSION

The derived analytic results for the probability distribution of mRNAs and proteins in the strong interaction limit and derived expression for large deviation function for protein production rate can provide significant insights into the role of sRNAs in regulating stochastic gene expression. These results can serve as building blocks for the analysis of more complicated genetic circuits involving sRNAs and the approach developed can potentially be generalized to analyze stochastic models of gene regulation with non-linear interaction.

REFERENCES

[1] Elowitz MB, et al. (2002). Science 297, 1836.
[2] Kaern M, et al. (2005) Nat. Rev. Genet. 6,451.
[3] Ebert MS and Sharp PA (2012) . Cell 149(3), 515-524.
[4] L Schmiedel JM, et al. (2015). Science 348, 128132.
[5] Alvarez-Garcia I and Miska EA (2005). Development 132 (21) 4653.
[6] Kumar N. et. al. (2016). Phys. Rev. E 94, 042419.
[7] Horowitz JM and Kulkarni RV (2017). Physical biology, 14(3), 03LT01.
[8] Levin E, et al. (2007). PloS Biology 5 (9) , e229 .