Quantifying negative feedback regulation by miRNAs

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***Short Abstract* — MiRNAs (miRNAs) play a crucial role in post-transcriptional gene regulation by pairing with target mRNAs to repress protein production. It has been shown that over one thirds of human genes are miRNA targeted [1]. Although hundreds of miRNAs have been identified in mammalian genomes, the function of miRNA-based repression in the context of gene regulation networks still remains unclear. In this article, we explore the functional roles of feedback regulation by miRNAs. In a model where repression of translation occurs by sequestration of mRNA by miRNA, we find that miRNA and mRNA levels are anti-correlated, resulting in larger fluctuation in protein levels than theoretically expected assuming no correlation between miRNA and mRNA levels. If miRNA repression is due to a kinetic suppression of translation rates, we analytically show that the protein fluctuations can be strongly repressed with miRNA regulation. We also discussed how either of these modes may be relevant for cell function.**

***Keywords* — micrRNA regulated gene expression, linear noise approximation.**

I. INTRODUCTION

MicroRNAs (miRNAs) are short (on average of 22 nucleotides long), non-coding RNA molecules that act as post-transcriptional regulators [1]. This form of regulation has been shown to be important during development, where they contribute to the maintenance of cell fates [2]. MiRNAs regulate gene expression by binding to target mRNA molecules at conserved sites in the 3' untranslated regions of mRNAs, ultimately leading to a reduction the levels of proteins encoded by the target mRNA [3]. Extensive evidence suggests that this suppression can occur in two possible ways: miRNAs sequester target mRNAs into large protein assemblies called P-bodies, where translation is suppressed and/or mRNAs are degraded. Alternately, miRNAs can act as translational repressors by blocking steps in initiation or elongation [4]. In either case, miRNAs can keep gene products at extremely low copy numbers, making them prone to noise [5]. Many miRNAs in the nervous system, where they are abundantly expressed, work in feedback circuits where they repress transcriptional activators or repressors that modulate their own production [6]. Although thousands of mammalian genes are potentially targeted by miRNAs [3], the functions of miRNAs in the context of gene networks are not well understood.

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II. RESULTS

We studied the dynamics of a negative feedback circuit consisting of a transcription factor (TF) that activates the production of a miRNA, which in turn acts as a translational repressor for the TF. This feedback circuit has been recently identified in neuronal precursor cells where it governs the differentiation of these cells into dopaminergic neurons [8]. We characterized and compared the steady-state and noise properties of the two different modes of action of miRNA in this circuit. In the first mode (sequestration), we find that miRNA and mRNA levels are anti-correlated which results in much larger fluctuations in the levels of the transcription factor than expected in a mean-field model where the miRNA and target mRNA levels are uncorrelated. This results in protein distributions that display long tails despite negative feedback. We then explored the impact of these long-tailed distributions on other genes downstream from the transcription factor. In the second mode, where miRNAs as kinetic suppressors of translation, we use the linear-noise approximation to analytically show that protein fluctuations can be strongly repressed by miRNA regulation as would be expected in a negative feedback circuit.

III. CONCLUSION

We find that the different mechanisms of miRNA-mediated translational repression in the feedback circuit discussed above lead to different noise levels of protein expression. Hence, the functional role of miRNAs may determine the expression pattern of genes downstream of the transcription factor. Our results suggest that cells may use these modes to determine cell fates in different contexts.

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