

A comparison of gene regulation by eukaryotic microRNAs and prokaryotic sRNAs

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Short Abstract —MicroRNAs (miRNAs) are short RNA sequences that regulate gene expression post-transcriptionally by binding to target mRNAs. Here we have developed a mathematical model of gene regulation by miRNAs. Our model reproduces the threshold-linear behavior of mean protein levels as a function of the miRNA level similar to experimental results. We use our model to calculate the intrinsic noise of miRNA-based gene regulation. We find that at the transition from the silenced to expressing regime, mRNA level becomes sensitive to small changes in the level of microRNA resulting in increased noise in gene expression. Despite the very different machinery and mode of action of miRNAs in eukaryotes and small non-coding RNAs (sRNAs) in prokaryotes, we find that they have similar gene expression properties for both mean protein levels as well as noise. Finally, motivated by the competing endogenous RNA hypothesis (ceRNA), we study the crosstalk between multiple mRNAs and argue that noise in gene expression may be a more sensitive measure of crosstalk than mean protein levels.

Keywords — MicroRNA, mRNA, noise, ceRNA, catalytic, stoichiometric

I. MOTIVATION

MICRORNAs (miRNAs) are short non-coding sequences of genes that post-transcriptionally regulate gene expression by binding target mRNAs. After transcription, miRNAs are processed by the Dicer machinery and incorporated into the RISC complex. The RISC complex binds mRNAs with specificity arising from complementary pairing between the miRNAs and target mRNAs. We consider the case where the miRNA targets mRNAs for cleavage resulting in a down-regulation of gene expression. Unlike small non-coding RNAs (sRNAs) in prokaryotes, the eukaryotic miRNAs are thought to function catalytically with a single miRNA-Risc complex degrading multiple mRNAs.

Recent experiments [1] suggest that miRNAs-based gene regulation shows threshold-linear behavior in the mean protein expression similar to bacterial sRNAs. In this work we consider a general, three-species model of post-transcriptional gene regulation by RNAs that reduces to regulation by miRNAs and sRNAs in certain limits. This allows us to compare gene regulation by miRNAs and sRNAs. We also use the model to investigate the competing RNA hypothesis (ceRNA) [2], in which crosstalk between different mRNAs takes place due to a limited pool of microRNA.

II. RESULTS

Using the linear noise approximation [3] and Gillespie algorithm [4], we detect a linear-threshold behavior in mean protein production. We derive analytic expressions for the noise in the repressing regime where proteins are expressed at low levels and find that noise is reduced due to a reduction in the effective burst size. In the crossover regime at which mRNA number is comparable to a “normalized” level of microRNA, we find a peak in protein noise similar to that found for bacterial sRNAs [5-7]. We also find that increasing the catalytic activity in miRNA regulation results in increased gene expression noise. Taken together, these results suggest that microRNAs are likely noisier than bacterial sRNA's even though they work catalytically rather than stoichiometrically. Finally, to investigate the ceRNA hypothesis, we extended the model of miRNA-based gene regulation to consider the case where a single miRNA regulates multiple mRNA species. Our model suggests that noise may be a more sensitive measure of crosstalk than mean protein numbers.

III. CONCLUSION

MicroRNA's regulate mRNAs in a catalytic process mediated by the miRNA-RISC complex. In contrast, bacterial sRNAs bind to mRNA via the chaperone protein Hfq and act stoichiometrically to regulate gene expression. Despite these fundamental differences, both systems exhibit a linear threshold behavior in their mean protein production and similar noise profiles. This suggests that gene regulation by non-coding RNAs in bacteria and eukaryotes may be indicative of convergent evolution. Finally, we have investigated the ceRNA hypothesis using our model and found that gene expression noise may be a more sensitive indicator of crosstalk than mean protein numbers.

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