In-sequence coding of noise in gene expression

Enrique Balleza[1,2], Lisa F. Marshall[3], J. Mark Kim[1], and Philippe Cluzel[1,4]

It is well established that, under nutrient rich conditions, stochastic transcription governs noise in gene expression. Surprisingly, we have identified a novel source of noise during translation elongation when bacteria grow in nutrient limited conditions. We demonstrate that the observed noise can be modulated by the choice of synonymous codons. Using a two-color reporting system, we show that this source of noise does not depend on fluctuations of common resources available to the translation machinery. Rather, we propose that ultrasensitivity in the tRNA charging/discharging cycle is the mechanism responsible for the observed noise.

***Keywords* — selective charging, nutrient limitation, gene expression noise**

I. Background

GENETICALLY identical cells exposed to homogeneous environmental conditions can exhibit dramatically different levels of gene expression [1,2]. High quality data combined with mathematical modeling has now yielded a common physical framework for cell-to-cell variability in gene expression [3,4]. This variability—termed *noise*—was found to arise from Poisson statistics reflecting bursts of transcription. These bursts are governed by either small numbers of mRNA being transcribed [4] or infrequent activation of promoters [3,5]. In all of these stochastic models, it is generally assumed that transcription but not translation governs noise.

Unexpectedly, our results reveal that, during nutrient limitation, *translation*, and not transcription, can instead be the dominant source of noise.

II. Results

At the population level, we demonstrated that the usage of "*robust*-to-starvation" or "*sensitive*-to-starvation" synonymous codons can modulate translation rate by up to two orders of magnitude when cells starve for the cognate amino acid [6]. With single-cell experiments, we show that not only the average expression changes but that there is an associated noise that depends on the synonymous codon and the concentration of the cognate amino acid. We exclude the possibility that transcription noise underlies the observed variability with two control experiments in which, using a single type of robust codon and a fixed amino acid concentration, we change i) the translation initiation rate and ii) the transcription rate of a fluorescent reporter. The control experiments confirm the expectation that noise driven by transcription bursts follow Poisson statistics *even* during nutrient limitation: i) noise is independent from translation initiation rate and ii) noise increases as transcription decreases. *A priori* the method for changing translation rate should not affect the previous results. However, when we change translation rate by using different synonymous codons the associated noise varies. In fact, the noise associated to sensitive codons displays a magnitude comparable to the transcription noise obtained in the control experiment.

In order to decipher the origin of the observed noise we used a dual-reporter: a polycistronic transcript composed of a "sensitive" (blue) and a "robust" (yellow) fast maturing fluorescent proteins [7]. We find that as the limiting amino acid concentration becomes lower, extrinsic noise dominates but decreases and, when the total noise is maximal, the intrinsic noise presents a maximum indicating that the observed single-cell variability comes from a codon-specific effect.

To explain these results, we hypothesize that the observed noise takes its origin in the ultrasensitivity of the tRNA charging/discharging cycle. We show that in fact the observed noise from a sensitive codon can be shifted to different amino acid concentrations by overexpressing the cognate tRNAs.

III. Conclusion

Life in resource-rich conditions is more the exception than the rule. Cells compete and strive in resource-limited environments, thus making the translation noise here uncovered an alternative bet-hedging strategy.

[1]FAS Center for Systems Biology, Department of Molecular and Cellular Biology, Harvard University, Cambridge, Massachusetts, USA.
[2]E-mail: enrique.balleza@gmail.com
[3]Seres Therapeutics, Cambridge, Massachusetts, USA.
[4]E-mail: cluzel@mcb.harvard.edu

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