Homeostasis of Protein and mRNA Concentrations in growing cells

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***Short Abstract* — Many experiments show that the concentrations of protein and mRNA fluctuate but on average are constant in growing cells, independent of the genome copy number. However, models of stochastic gene expression often assume constant gene expression rates that are proportional to the gene copy numbers, which are therefore incompatible with experiments. Here, we construct a minimal gene expression model to fill this gap. We show that (1) because the ribosomes translate all proteins, the concentrations of proteins are regulated in an exponentially growing cell volume; (2) the competition between genes for the RNA polymerases makes the gene expression rate independent of the genome number; (3) the fluctuations in ribosome level and cell density can generate a global extrinsic noise in protein concentrations; (4) correlations between mRNA and protein levels can be quantified.**

***Keywords* — Gene expression; Cell size regulation; Biophysics**

Despite the noisy nature of gene expression [1,2], various aspects of single cell dynamics, such as volume growth, are effectively deterministic. Recent single-cell measurements show that the growth of cell volumes is often exponential. These include bacteria [3], budding yeast [4] and mammalian cells [5]. Moreover, the mRNA and protein numbers are on average proportional to the cell volume throughout the cell cycle [5-7]. Therefore, the homeostasis of mRNA concentration and protein concentration is maintained in an exponentially growing cell volume. The exponential growths of mRNA and protein number indicate dynamical transcription and translation rates proportional to the cell volume, and also independent of the genome copy number. However, current gene expression models often assume a fixed cell volume with constant transcription and translation rates, which are proportional to the gene copy number. Therefore, fixed cell volume models fail to reveal how cells keep constant mRNA and protein concentrations as the cell volume grows and the genome is replicated.

The homeostasis of protein and mRNA concentrations imply that there must be a regulatory mechanism in place to prevent the accumulation of noise over time and to maintain a bounded distribution of concentrations. The goal of this work is to identify such a mechanism by developing a genome-wide coarse-grained model taking into account explicitly cell volume growth. We will consider an idealized cell in which genes are constitutively expressed for simplicity. The ubiquity of homeostasis suggests that the global machineries of gene expression, RNA polymerases (RNAPs) and ribosomes, should play a central role within the model. Indeed, the exponential growth of cell volume, protein and mRNA number originates from the auto-catalytic nature of ribosomes, the limiting factor in the translational process. The bounded distributions of concentrations are a result of the fact that ribosomes make all proteins. The independence of the mRNA concentration of the genome copy number is a natural result of the limiting nature of RNAP in the transcriptional process in which genes are competing for this global resource. Furthermore, we attempt to identify candidates for the global extrinsic noise, which sets the lower bound of noise in protein concentrations. Within our model, the only two possibilities are the fluctuations in ribosome levels and cell volume growth rate. We show that these two mechanisms lead to distinct correlation patterns between protein levels, therefore providing a method to determine the dominant contribution to the global extrinsic noise from experimental data.

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