Review

Interplay between gene expression noise and regulatory network architecture

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Complex regulatory networks orchestrate most cellular processes in biological systems. Genes in such networks are subject to expression noise, resulting in isogenic cell populations exhibiting cell-to-cell variation in protein levels. Increasing evidence suggests that cells have evolved regulatory strategies to limit, tolerate or amplify expression noise. In this context, fundamental questions arise: how can the architecture of gene regulatory networks generate, make use of or be constrained by expression noise? Here, we discuss the interplay between expression noise and gene regulatory network at different levels of organization, ranging from a single regulatory interaction to entire regulatory networks. We then consider how this interplay impacts a variety of phenomena, such as pathogenicity, disease, adaptation to changing environments, differential cell-fate outcome and incomplete or partial penetrance effects. Finally, we highlight recent technological developments that permit measurements at the single-cell level, and discuss directions for future research.

Gene expression noise

Random fluctuations in expression levels of individual proteins are inevitable. These fluctuations are the result of the intrinsically stochastic nature of molecular interactions that underlie transcription, translation and post-translational regulation [1–7]. This results in cell-to-cell variation in protein expression levels within clonal cell populations, despite a homogeneous environment, a phenomenon referred to as 'gene expression noise' or 'stochasticity' [1–7]. In a more general sense, expression noise may also refer to cell-to-cell variation in the abundance of biomolecules, such as mRNA. Gene expression noise was first described during the second half of the 20th century [3,4]. However, with recent advancements in single-cell

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Glossary

Bistable system: a system for which two alternative stable states exist.
Clonal cell population: a population of cells derived from a single mother cell that share identical genomic contents (i.e. without mutations).
Expression noise: stochastic fluctuations in the protein level of a gene within a clonal cell population maintained in a homogeneous environment. Noise is generally defined as the coefficient of variation (CV); that is, the ratio between standard deviation and mean value of protein abundance for a given gene in a population of cells. In a more general sense, expression noise may also refer to variation in the abundance of biomolecules, such as mRNA.
Extrinsic noise: gene-independent fluctuations that can be attributed to variations in external factors influencing the expression of a set of genes (e.g. pathway specific) or globally. Extrinsic noise can be influenced at a local level by the abundance of TFs and at a global level by the abundance of gene expression machinery (e.g. ribosome abundance).
Fluctuating environment: an environment whose physical, chemical and nutritional components are subjected to frequent variations.
Gene circuit: a small number of genes influencing the expression of one another via regulatory interactions.
Gene regulatory network (GRN): a network representation of gene regulatory events, in which nodes are genes and regulatory interactions are links. Such interactions include transcriptional regulation and post-translational modifications.
Intrinsic noise: gene-specific fluctuations that can be attributed to the stochastic fluctuations in the different steps of the expression process of a specific gene. Factors contributing to intrinsic noise include the promoter structure of the gene, its localization within the chromosome and the nuclear architecture.
Monostable system: a system for which only one stable state exists.
Network architecture: a pattern of links connecting the nodes of a network.
Network motif: a recurrent pattern of interconnections in a network that appear more frequently than expected by chance in random networks of similar size.
Noise propagation: stochastic expression of a target gene resulting from gene expression noise in upstream regulatory genes, within a given circuit.
Phenotypic buffering or capacitance: a phenomenon where individuals in a population produce the same phenotype despite genetic or environmental variation. Hsp90 is an example of a phenotypic buffer that can mask the effect of mutations in their substrate proteins.
Retroactivity: alteration in the dynamic behavior of a gene circuit owing to the connectivity of its output gene with downstream circuits.
Stable and/or steady state: in the context of a regulatory interaction, the steady-state expression level describes a narrow range of expression levels within which target gene abundance is maintained despite small perturbations in the expression of its regulatory TF. This will depend on the kinetics of synthesis and degradation of the target gene.
TATA-box: consensus DNA sequence 5′-TATAAA-3′ found within the proximal and/or core promoter of approximately a quarter of the genes in eukaryotes and archaea. This sequence is typically bound by the TATA-box binding protein to initiate transcription by the RNA polymerase.

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Transcriptional burst: bursts of mRNA production resulting from the promoter of a gene switching between periods of prolonged inactive (or 'off') states and short-lived active (or 'on') states.
Transcriptional regulatory network: a network representation of transcriptional events where nodes represent TFs and TGs and links denote regulatory interactions between TFs and TGs, mediated by the binding of a TF to the promoter region of its TG.

and single-molecule techniques, it has become possible to quantify its extent and better grasp its importance. These approaches have revealed that the expression level of a gene can drastically vary between individual cells, exhibiting stochastic fluctuations that can span up to six orders of magnitude [5].

The past decade witnessed a renewed interest in understanding the significance of expression noise in synthetic gene circuits [5,8,9]. These studies revealed that genes in such circuits were subject to fluctuations in the amplitude, frequency and timing of their expression, as a result of stochastic effects during the process of gene expression. Subsequent experiments dissected the characteristics of noise and defined its intrinsic and extrinsic components [6,7] (Box 1). Research is now also aimed at understanding how expression noise is handled within gene regulatory networks (GRNs), which control the transcriptional, signaling and developmental programs in cells [5,10].

Several excellent reviews describe key experiments and concepts pertaining to the molecular mechanisms that generate expression noise in a gene [2,11,12] (Box 2). In this review, we focus on the interplay between gene expression noise and the architecture of gene regulatory networks at different levels of organization (Figure 1a). This interplay is linked to a fundamental question that the field is just beginning to address: how does expression noise influence the ability of a GRN to relay information accurately and robustly (i.e. convert variations in its inputs into appropriate responses in its outputs)? Here, we synthesize the current knowledge on how GRN architecture handles the trade-off between information transfer and

Box 1. Quantification of expression noise

Expression noise can be quantified using a fluorescently tagged version of a protein of interest, and measuring the distribution of normalized fluorescence intensities across a population of clonal cells in a stable environment (Figure I). Noise is generally defined as the squared coefficient of variation of the fluorescence levels (SCV = $(\sigma/\mu)^2$). This dimensionless value basically reflects how large the standard deviation (σ) of expression levels is compared to the mean expression level (μ). Alternative measures of noise have also been proposed or used, e.g. coefficient of variation (CV = σ/μ), Fano Factor ($F_{\Delta t} = (\sigma^2/\mu)_{\Delta t}$) or distance from the median CV (DM) [110]. Expression noise can be decomposed into intrinsic and extrinsic components [7,111]. The measurement of intrinsic and extrinsic noise of a gene x requires the use of double reporter systems in which two identical promoter regions regulate two distinct fluorescent reporter genes (in Figure I, x-GFP and x-RFP). In the case of intrinsic noise, each reporter fluctuates independently of the other. In the case of extrinsic noise, the fluctuations in fluorescence of the two reporters co-vary.

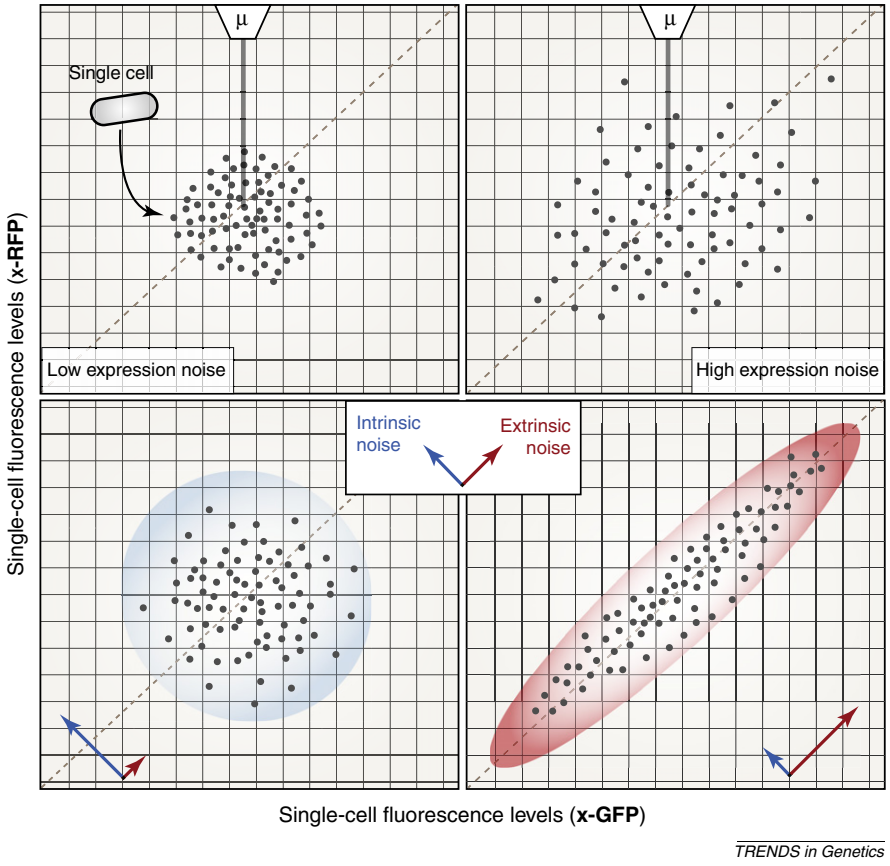

Figure I. Quantification of expression noise.