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INTRODUCTION TO QUANTITATIVE BIOLOGY

Noise in gene expression - summary of Elowitz et al. (2002)

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Stochastic Gene Expression in a Single Cell

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The amount of protein produced by a particular gene varies from cell to cell.

The **noise** (defined as the standard deviation divided by the mean) in this distribution is often called coefficient of variation (CV) and be divided into two components.

EXTRINSIC AND INTRINSIC NOISE

"Because expression of each gene is controlled by the concentrations, states, and locations of molecules such as regulatory proteins and polymerases, fluctuations in the amount or activity of these molecules cause corresponding fluctuations in the output of the gene. " —> **Extrinsic noise**

"On the other hand, consider a population of cells identical not just genetically but also in the concentrations and states of their cellular components. Even in such a (hypothetical) population, the rate of expression of a particular gene would still vary from cell to cell because of the random microscopic events that govern which reactions occur and in what order." —> **Intrinsic noise**

Intrinsic noise is *"that remaining part of the total noise arising from the discrete nature of the biochemical process of gene expression. No matter how accurately the levels of regulatory proteins are controlled, intrinsic noise fundamentally limits the precision of gene regulation."*

EXPERIMENTAL DESIGN

Operationally, intrinsic noise for a given gene may be defined as the extent to which the activities of two identical copies of that gene, in the same intracellular environment, fail to correlate (Fig. 1, A and B). Therefore, we built strains of *Escherichia coli*, incorporating the distinguishable cyan (*cfp*) and yellow (*yfp*) alleles of green fluorescent protein in the chromosome. In each strain, the two reporter genes were controlled by identical promoters. To avoid systematic differences in copy number, we integrated the genes at loci equidistant from, and on opposite sides of, the origin of replication (fig. S1). The two fluorescent proteins exhibited statistically equivalent intensity distributions and thus displayed the necessary independence and equivalence to detect noise (*7*).

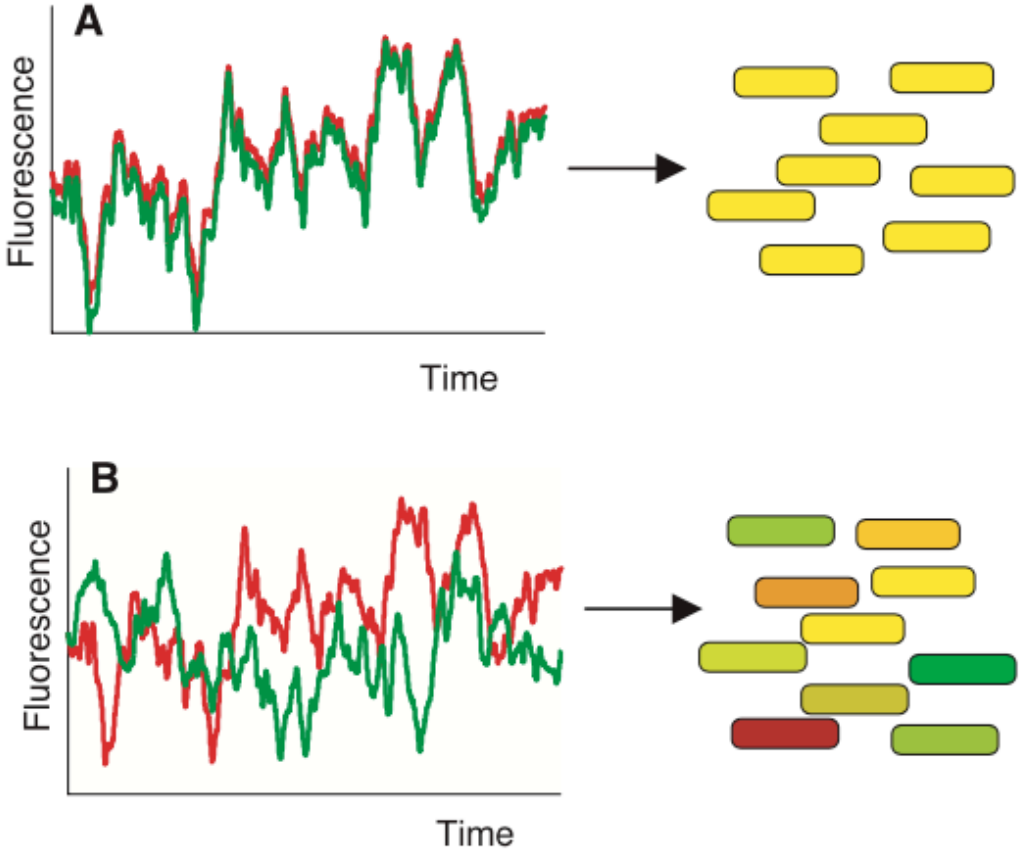
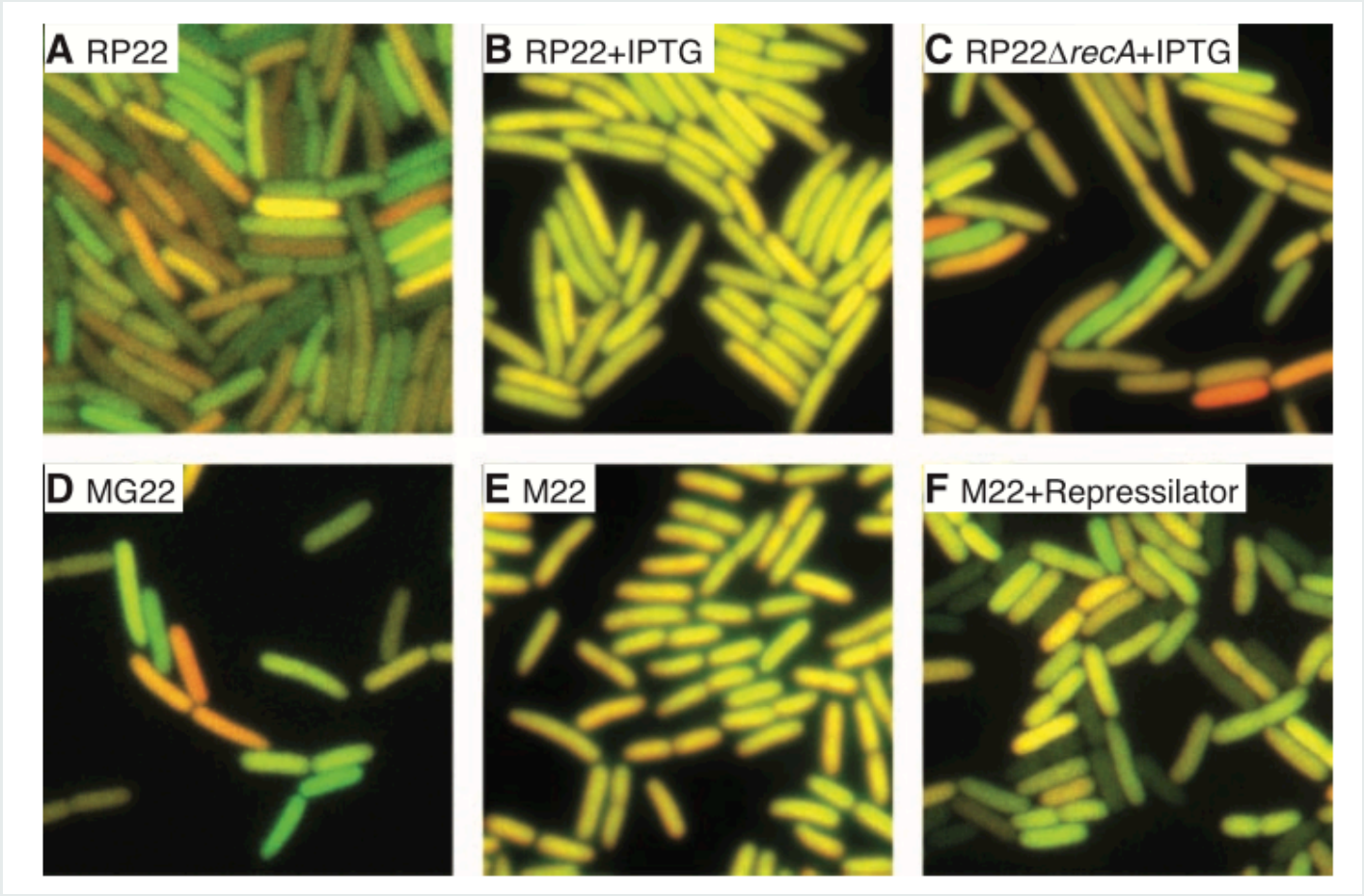


Fig. 1. Intrinsic and extrinsic noise can be measured and distinguished with two genes (*cfp*, shown in green; *yfp*, shown in red) controlled by identical regulatory sequences. Cells with the same amount of each protein appear yellow, whereas cells expressing more of one fluorescent protein than the other appear red or green. (**A**) In the absence of intrinsic noise, the two fluorescent proteins fluctuate in a correlated fashion over time in a single cell (left). Thus, in a population, each cell will have the same amount of both proteins, although that amount will differ from cell to cell because of extrinsic noise (right). (**B**) Expression of the two genes may become uncorrelated in individual cells because of intrinsic noise (left), giving rise to a population in which some cells express more of one fluorescent protein than the other.

EXPERIMENTS



…cells were grown in LB medium and photographed through cfp and yfp fluorescence filter sets and in phase contrast.

OBSERVATION

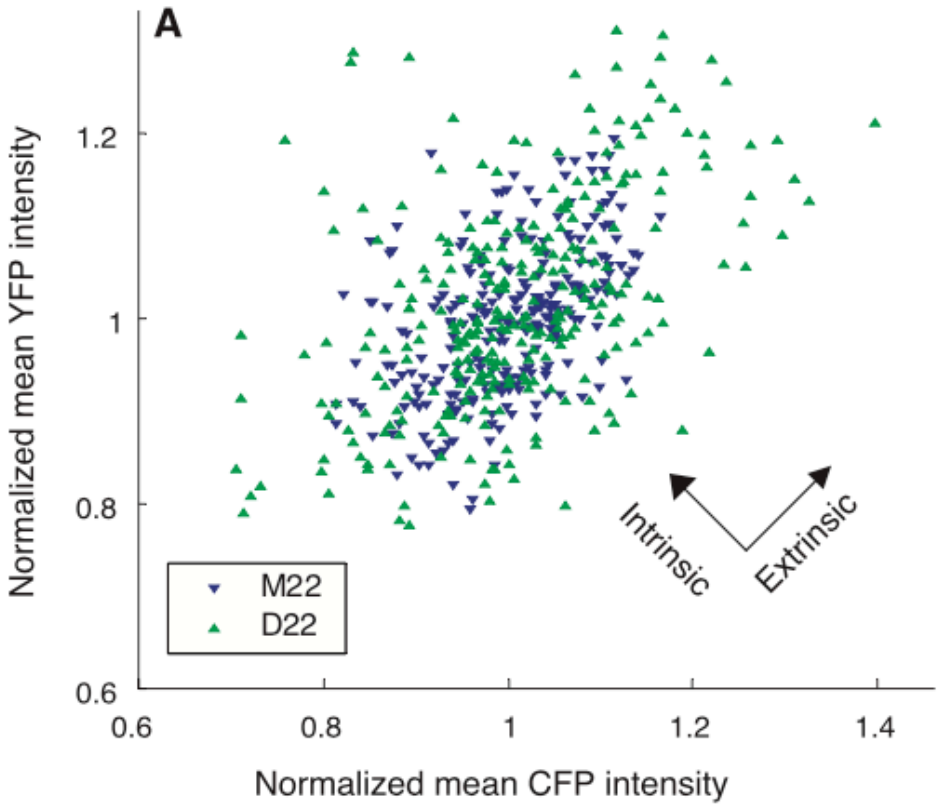


Fig. 3. Quantification of noise. (**A**) Plot of fluorescence in two strains: one quiet (M22) and one noisy (D22). Each point represents the mean fluorescence intensities from one cell. Spread of points perpendicular to the diagonal line on which CFP and YFP intensities are equal corresponds to intrinsic noise, whereas spread parallel to this line is increased by extrinsic noise.