Course CBS530 Assignment No 1
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Analysis of the paper: Stochastic(noisy) Gene Expression in a Single Cell by Elowitz et al

Abstract

In this report the author gives her own view on the recent article of Elowitz et al[1]. The author shall try to cover the question that the work of this paper addressed, a critique of the appropriateness of the methodology, the primary results that relate to the question and the discussion of whether the data answer the question.

The objective of this paper is to determine the total variation (that is defined as standard deviation divided by the mean) given mathematically as ($n_{tot}^2 \equiv \frac{\langle c^2+y^2\rangle - 2\langle c\rangle\langle y\rangle}{2\langle c\rangle\langle y\rangle}$). This is divided into Intrinsic noise (biochemical process of gene expression) mathematically defined as ($n_{int}^2 \equiv \frac{\langle (c-y)^2\rangle}{2\langle c\rangle\langle y\rangle}$) and Extrinsic noise (fluctuation in cellular components) mathematically given as ($n_{ext}^2 \equiv \frac{\langle cy\rangle - 2\langle c\rangle\langle y\rangle}{\langle c\rangle\langle y\rangle}$).

Some questions arise from this article are: What is the effect of Intrinsic and Extrinsic class of noise on cell-cell variation ? Whether cell-cell variation is causing by intrinsic and extrinsic noise or not ? Given the substantial amount of noise what will be the condition of cells ? How much (both) noise are occurring in all the intracellular reactions ? Weather noise effects the heterogeneity in a clonal population or not ? Is extrinsic noise depends upon intrinsic noise or vice versa ? How noises depends upon rate of transcription ?

They showed that the intrinsic and extrinsic noise can be measured and distinguished with two genes of intensities cfp (green) and yfp (red). In two strain one quite (M22) and one noisy (D22) cfp and yfp intensities are different corresponding to intrinsic and extrinsic noise. In the same intracellular environment intrinsic noise with two identical copies of gene fail to correlate so they constructed strain of Escherichia.coli (E.coli) for detection of noise. They have shown that intrinsic and extrinsic noise contribute overall variation. By experiment they showed that noise in E.coli using different strain with modification shows different level of intrinsic, extrinsic and total variation, and then cell exhibit different level of noise. Cells appear in different color with different amount of fluorescent protein. In the absence and presence of intrinsic noise the two fluorescent protein shows correlated fashion in a single cell and uncorrelated in individual cells and amount of protein vary from cell to cell because of extrinsic noise.

They measured the input of noise to gene expression and output of noise with sources of extrinsic noise that is varying from cell to cell. Intrinsic noise arises from discrete nature of biochemical process of gene expression and intrinsic noise fundamentally limits the accuracy of gene regulation. They showed by measurement that how cells are going through the process of intensities and both noise could be determined from plots of cfp versus yfp fluorescence intensity in individual cells. Note that n_{int} indicates the mean relative difference in fluorescence intensity, because n_{int} and n_{ext} make orthogonal contribution to the total noise n_{tot}, so these are satisfying the

Pythagoras relation $n_{int}^2 + n_{ext}^2 = n_{tot}^2$ (CFP=YFP) (Note that the Pythagoras relation tells that In triangle ABC, if $\angle B = 90$ then we have $a^2 + c^2 = b^2$).

Rate of expression of a particular gene vary from cell to cell because of random microscopic events (that govern which reactions occur and in what order). They have checked the different noise levels at rate of transcription. When they moved the reporter into several E.coli both intrinsic and extrinsic noise increases this is at reduction of transcription rate, increase in the noise indicate the presence of cell- cell variation. At intermediate rate of transcription, n_{int} decrease monotonically, n_{ext} displays a maximum. n_{ext} is substantially varying from cell to cell carrying a different copies of modification.

To understand the behavior of transcriptional regulatory circuits they introduced some network, they found regulatory dynamics can cause substantial changes in noise level. Intrinsic noise fundamentally limits the precision of gene regulation no matter how accurately the levels of regulatory protein are controlled. Intrinsic and extrinsic noise effect the overall variation. They came to know that intrinsic and extrinsic classes of noise are important in setting cell-cell variation in gene expression. Both type of noise should similarly occur in all other intracellular reactions. They told that noise, if amplified offers the opportunity to generate long term heterogeneity in a clonal population. So total cell-cell variability (n_{tot}) does not uniquely determine intrinsic noise. If the amount of noisiness in a cell is genetically determined, then different strains might exhibit different intrinsic and extrinsic noise levels.

To determine the noise in vivo, they did some experiments with some strains they found results that indicates:

- Constitutive gene expression can be uniform under some conditions.
- Low noise state does not strictly depend on a particular promoter sequences.

Finally they showed transcription rate (the rate at which RNA polymerase transcribes the gene into molecules of messenger RNA (mRNA)), regulatory dynamics, and genetic factors (related to genes) control the amplitude of noise. By these result they have established foundation for modeling noise in genetic. Stochastic effects play crucial role in biological processes such as development, amplified by feedback mechanism and determine cell fates.

Stochastic gene expression models predict that intrinsic noise should increase as the amount of transcript decrease. For any particular gene, it remains unknown weather cell-cell variation is set by noise in expression of the gene itself or by fluctuations in the amount of other cellular components.

References

[1] Michael B. Elowitz, A. J. Levine, E. D. Siggia and P. S. Swain, *Stochastic gene expression in a single cell.* Science **16** (August 2002).