# Protein Fluctuations in Single Cells and Population Variability

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***Short Abstract* — The copy number of any protein vary among cells even in a genetically homogenous population. Characterizing and understanding this variation and its sources is a fundamental problem in biophysics. We have recently shown that the protein distributions measured under a broad range of biological realizations collapse to a single non-Gaussian curve under scaling by the first two moments. Here we show that this distribution is a result of the cellular dynamics, which can be well characterized through single-cell measurements of protein expression. This dynamics exhibit wide range of time-scales and reveal epigenetic inheritance patterns.**

***Keywords* —Variability in protein content, protein expression dynamics.**

## I. Background

We have recently studied the universal aspects of protein distributions in clonal populations of microorganisms by comparing the population distributions over a wide range of biological realizations [1]: (a) Two archetypical microorganisms, bacteria and yeast, with two well-studied regulatory systems: the LAC operon in E. coli and the GAL system in S. cerevisiae. Both systems were studied under strong activation conditions. (b) Different metabolic growth conditions: the organisms were grown in chemostats – continuous culture in steady state and transients, as well as in batch cultures. (c) Highly regulated versus constitutive expression: the regulated LAC and GAL systems were compared to constitutively expressed proteins in both organisms. (d) Different promoter copy numbers: the same regulatory systems were placed on high-copy and low-copy number plasmids as well as integrated into the genome in a single copy. (e) Reporter Green Fluorescent Protein (GFP) was compared to an essential functional tagged-protein controlled by the same promoter. The spectrum of our experiments spans an array of "control parameters" which covers many of the essential processes affecting protein content in cells. In addition, the two organisms used, E. coli and S. cerevisiae, are distinct in almost every aspect of their cell biology and life style. Yet remarkably, the broad protein distributions measured under this broad range of biological realizations were shown to collapse to a single non-Gaussian curve under scaling by the first two moments—subtracting the mean and dividing by the standard deviation [1]. Moreover, in all experiments the variance was found to depend quadratically on the mean, suggesting that a single degree of freedom determines the entire distribution. These results imply that protein fluctuations do not reflect any specific molecular or cellular mechanism, and suggest that the observed distributions result from continuous cellular dynamics rather than from statistics over an ensemble of realizations in single cells.

## II. Results

To test this hypothesis, we have measured the amount of protein in a single bacterial cell over an extended period of time (~100 generations). This was achieved using a microfluidic device to trap bacteria and follow their growth under constant condition.

Our results show that indeed protein fluctuations measured at the single-cell level exhibit the same distribution as that measured in a population. In addition, also here the variance-to-mean relationship exhibits similar functional form as before. However, the single-cell measurements do not cover the same range as the population, which could be due to limited sampling rate and/or finite lifetime of the cell.

These results already show that the variability among individuals in a genetically homogenous population does not reflect discrete stable cellular states, but are rather a reflection of a rich continuous expression dynamics, which we find to consist of a wide range of time scales, some of which extend over ~10 generation.

## III. Conclusions

Our results suggest that in order to understand protein distributions in populations of microorganisms, the population cannot be regarded as a statistical ensemble of cells with separate realizations, as the cells exhibit long-term correlations, and slow modes of gene expression. These correlations and gene expression modes are revealed in the single-cell measurements of protein expression, which also exhibit rich dynamics that is yet to be understood.

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## References

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