# 186. Heterogeneity in Protein Expression Induces Metabolic Variability in a Modeled *Escherichia coli* Population

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**Project Goals: Methodology used to develop whole cell models of methanogens will be applied to the model organism *E. coli* for which considerable single cell proteomics and kinetic data have just become available. The integration of the effects of stochastic gene expression with genome-scale metabolic/regulatory models is a novel contribution to systems biology. Besides helping to elucidate the underlying mechanisms by which cells respond to intrinsic noise with differential usage of metabolic pathways, the method could be put to practical use in synthetic biology and bioengineering applications. The goal of this project is to validate the computational methodology for analyzing the effect cellular noise have on population heterogeneity within monoclonal populations and demonstrate its applicability to *E. coli*.**

Stochastic gene expression can lead to phenotypic differences among cells even in isogenic populations growing under macroscopically identical conditions [1]. Here flux-balance analysis is applied in investigating the effects of single cell proteomics data on the metabolic behavior of an *in silico E. coli* population. The latest metabolic reconstruction is integrated with transcriptional regulatory data in order to model realistic cells growing in a glucose minimal medium under aerobic conditions. Our modelled cells exhibit a broad distribution of growth rates (Figure 1). Well-defined subpopulations that differ in terms of pathway usage can be identified using principal component analysis. The population differentiates into slow-growing acetate- secreting cells and fast-growing $CO_2$- secreting cells, with a large population growing at intermediate rates shift from glycolysis to Entner-Doudoroff (ED) pathway usage (Figure 2). Constraints on pathway usage imposed by integrating transcriptional data have a large impact on NADH oxidizing pathway usage within the cell. Finally, stochasticity in the expression of only a few genes may be necessary to capture most of the metabolic variability seen in the entire population (Figure 3).

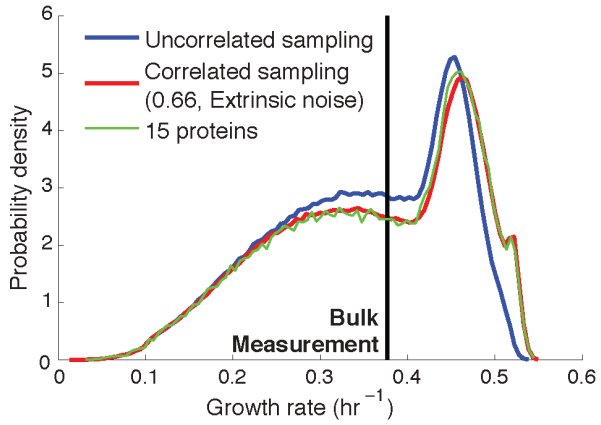


**Figure 1 Distributions of specific growth rates predicted by uncorrelated protein sampling (blue), by imposing correlations of correlation coefficient 0.66 among proteins in the extrinsic noise regime (red), and by sampling only the 15 proteins whose copy numbers are most likely to constrain the growth of modeled cells (green). The black line represents the experimentally determined bulk specific growth rate.**

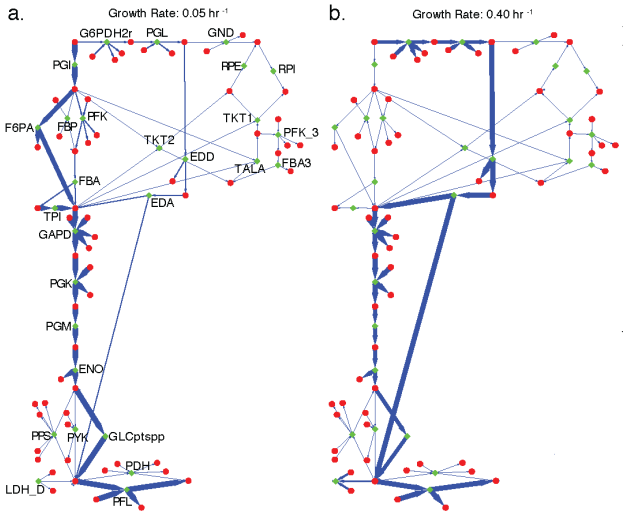


**Figure 2 Examples of differences in usage between glycolysis and the ED pathway by representative cells in our metabolize the same amount of glucose as glycolysis, but at the cost of substrate-level ATP generation. Slowgrowing cells tend to use glycolysis (a), whereas intermediate to fast-growing cells tend to use the ED pathway (b).**

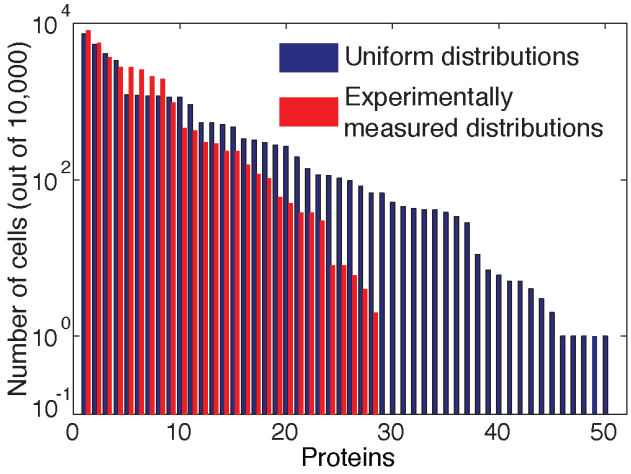


**Figure 3 Bar graph indicating the number of cells whose growth is directly limited by a given protein. Only 28 proteins sampled from the experimentally measured protein distributions (shown in red) limit the growth rate of at least one cell in a population of 10,000. For reference, over 50 proteins would be expected to limit the growth rate of at least one cell, had all enzyme counts been sampled from a uniform distribution from 1 to 1,000 (shown in blue).**

## References

1) P. Labhsetwar, J.A. Cole, E. Roberts, N.D. Price, Z. Luthey-Schulten. *Proc. Nat. Acad. Sci.*, 110(34):14006-11, 2013.

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