A Dynamic View of Phenotypic Variability in Cell Populations

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Cells in a population exhibit variability in shape, size, molecular content and many other phenotypic properties. How this variability reflects the processes of growth, protein production, division and inheritance is still largely an open question. Here we utilize experimental methods that trace individual bacteria for hundreds of growth and division cycles, to shed light on the dynamic basis of phenotypic variability. We compare phenotypic distributions over time in single cells to distributions across a cell population. Scaled fluctuations of both cell size and highly-expressed protein content are found to be universally distributed, and collapse on a typical skewed non-Gaussian distribution shape. Additionally, a tight quadratic relation between mean and variance of these distributions is found, both in temporal and in population statistics. These findings indicate a strong buffering of the population level from microscopic processes, and can be explained by an effective, mesoscopic-scale model of growth, division and homeostasis. In contrast, time-averaged cell size and protein content can remain distinct among individual cells over many generations, breaking the ergodicity often assumed to hold in cell populations. This individuality can be traced back to extremely slow dynamics, with typical timescales of more than 100 generations. Correlations among single-cell variables reveal effective homeostasis mechanisms that are also distinct among individual cells, and suggest a global simultaneous homeostasis of multiple phenotype components. Thus, the cell population is both coupled to and buffered from the complex internal cellular processes. Our results taken together suggest that the cell population is better viewed as a fundamental level of biological organization, rather than a statistical ensemble of cells.

REFERENCES

[1] H. Salman, N. Brenner, Ch-K. Tung, N. Elyahu, E. Stolovicki, L. Moore, A. Libchaber and E. Braun, "Universal protein fluctuations in microorganism populations". *Phys. Rev. Lett*. **108**, 238105 (2012).

[2] N. Brenner, E. Braun, A. Yoney, L. Susman, J. Rotella and H. Salman, "Single-cell protein dynamics reproduce universal fluctuations in cell populations". *Eur. Phys. J. E* **38**, 102 (2015).

[3] N. Brenner, C.M. Newman, D. Osmanovic, Y. Rabin, H. Salman and D. Stein, "Universal Protein Distributions in a Model of Cell Growth and Division", *Phys. Rev. E* **92**, 042713 (2015).

[4] L. Susman, M. Kohram, H. Vashistha, J. T. Nechleba, H. Salman and N. Brenner, "Individuality and slow dynamics in bacterial growth homeostasis", Arxiv preprint (2018).

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