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Single-Cell-Based Analysis Highlights a Surge in Cell-to-Cell Molecular Variability Preceding Irreversible Commitment in a Differentiation Process

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In some recent studies, a view emerged that stochastic dynamics governing the switching of cells from one differentiation state to another could be characterized by a peak in gene expression variability at the point of fate commitment. We have tested this hypothesis at the single-cell level by analyzing primary chicken erythroid progenitors through their differentiation process and measuring the expression of selected genes at six sequential time-points after induction of differentiation. In contrast to population-based expression data, single-cell gene expression data revealed a high cell-to-cell variability, which was masked by averaging. We were able to show that the correlation network was a very dynamical entity and that a subgroup of genes tend to follow the predictions from the dynamical network biomarker (DNB) theory. In addition, we also identified a small group of functionally related genes encoding proteins involved in sterol synthesis that could act as the initial drivers of the differentiation. In order to assess quantitatively the cell-to-cell variability in gene expression and its evolution in time, we used Shannon entropy as a measure of the heterogeneity. Entropy values showed a significant increase in the first 8 h of the differentiation process, reaching a peak between 8 and 24 h, before decreasing to significantly lower values. Moreover, we observed that the previous point of maximum entropy precedes two paramount key points: an irreversible commitment to differentiation between 24 and 48 h followed by a significant increase in cell size variability at 48 h. In conclusion, when analyzed at the single cell level, the differentiation process looks very different from its classical population average view. New observables (like entropy) can be computed, the behavior of which is fully compatible with the idea that differentiation is not a "simple" program that all cells execute identically but results from the dynamical behavior of the underlying molecular network.http://journals.plos.org/plosbiology/article?id=10.1371/journal.pbio.1002585