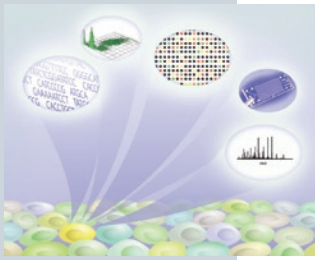
nature methods

Supplement on single-cell analysis



The cover image depicts artistically the isolation and analysis of a single cell from within a heterogenous cellular population. Cover design by Erin Dewalt.

Biological systems are complex, and the cells that comprise them are, more often than not, molecularly and functionally distinct. This is true for the cells that make up a tissue in a multicellular organism—the highly heterogenous neurons of the human brain, for instance—but also for isogenic single-celled bacteria and for mammalian cells *in vitro*. Stem cells, in particular, are increasingly recognized as being divisible into subpopulations that, at least in some cases, have distinct functional properties.

Cellular heterogeneity may come about for several nonexclusive reasons: because of genetic or epigenetic differences, as a consequence of differing microenvironments or because there is a stochastic component to the molecular processes occurring in otherwise identical cells. Whatever the source, there are many circumstances in which heterogeneity is an inherent and also a desirable property of cells.

Many experimental analyses, however, are carried out on pools of cells and are consequently blind to heterogeneity in the population. Measurements of averages, by definition, smooth the differences out! One route to a finer-grained picture of complex biological systems is to make measurements on single cells. But whereas methods such as electrophysiology or high-resolution imaging intrinsically lend themselves to analysis of single cells, others—biochemical approaches to examine gene expression, protein levels or small-molecule distributions, for instance—must perform at very high sensitivity to measure the small quantities of material that can be extracted from a single cell.

Such measurements are beginning to be possible as discussed in this supplement, which reviews methods for single-cell analysis. Three Reviews and a Commentary describe methods for reading out genomes and for measuring transcript, peptide and metabolite levels in a single cell. Two Perspectives describe methods for the study of single stem cells.

We hope this collection is both practically useful and also stimulates thinking about the nature of biological heterogeneity and the ways in which single-cell analysis can help decipher it.

Natalie de Souza

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