

Preface

Cells play a significant role in our daily lives. However the intercellular interactions, intracellular behaviors, and environmental responses of cellular organelles are still not fully understood and the ensemble-averaged measurement of millions of cells together is not able to provide detailed information at the single-cell level. For example, the genome, epigenome, and transcriptome analyses of bulk cell populations are informative, however, they cannot reveal the heterogeneity and molecular dynamics within a certain cell population. Also, these analyses cannot provide any information about an underrepresented cell subpopulation that could have a differential or crucial function in a specific biological context, such as stem cells or tumor-initiating cells. In contrast, single cell sequencing (SCS) is able to empirically infer the driver mutations and map the sequential mutation events during cancer development. The integration of genomics and transcriptomics in single cancer cells will also provide valuable information about the functional consequences of mutations and the copy number variations in these cells. In the past few years, significant advances have been made in isolation of single cells, whole-genome or whole-transcriptome amplification and genome-wide analysis platforms, which not only allow high resolution genome and transcriptome analysis, but also have the potential to reveal the epigenome map of the target single cells. Undoubtedly, these novel approaches will produce profound health benefits, such as a more efficient treatment strategy for patients affected by genetic disorders, which can be realized at the single-cell level.

Apart from the considerable power of single-cell analysis (SCA), the huge amounts of data generated from the SCA process have emerged as a challenging issue. In recent years, bioinformatics techniques have been employed to study the “big data” from large ensembles of single cell data. Thus interestingly, some unresolved questions in the past can be answered now thanks to the unique information obtained from single-cell analysis, such as whether any two single cells are really the same if we are able to measure adequate parameters with sufficient accuracy. Are there two cells which have similar biological functions and predictable outcomes when treated with the same drugs or environmental factors?

SCA, without doubt, is an efficient and valuable approach to understand the fundamental biology in embryonic development, to provide detailed knowledge of the cell lineage trees in higher organisms, to dissect the tumor heterogeneity and disease, etc.

To analyze the cellular function, SCA can be performed by combining capillary electrophoresis (CE) with laser-induced fluorescence (LIF) detection, electrochemical detection (ED), flow cytometry or mass spectrometry, etc. Recently, with the development of microelectromechanical systems (MEMS) technology and its integration with chemical engineering, biomedical engineering, chemistry, material science, and life science, Bio-MEMS (sometimes considered synonymous with lab-on-a-chip (LOC) or micro total analysis systems (μ TAS)) has emerged as a powerful tool for more complex manipulations of chemical and biological agents in micro/nano fluidic environments. Micro/nanofluidic devices with the power to manipulate and detect bio-samples, reagents, or biomolecules at the micro/nanoscale can well fulfill the requirements of single-cell analysis. Thus, they are not only useful for cell manipulation, isolation, separation, and lysis, but are also able to easily control the biochemical, electrical, and mechanical parameters in SCA with precisely controlled dosage, spatial resolution, or temporal pace.

This book includes 15 chapters, covering a wide spectrum of the essential aspects of single-cell analysis. Contributed by experts in their own fields, these chapters provide technical tips based on valuable experience and knowledge. Potential problems and challenges as well as possible solutions are also discussed with an emphasis on the future prospects. “[Single-Cell Behavioral Assays for Heterogeneity Studies](#)” describes single cell behavioral assay for heterogeneity study using single cell isolation and tracking to investigate cell proliferation, differentiation, and lineage. There are two platforms being discussed that include the cell migration platform to measure cell motility, deformation, and invasiveness and the cell–cell interaction platform to study the alteration of cell behaviors caused by reciprocal interactions among cells. “[Systems Biology in Single Cells](#)” presents single-cell analysis in systems biology. It covers technologies that enable the isolation of individual cells in a form that accommodates systemics studies, the biological methods deployed on such isolated cells to generate system-level information, and the bioinformatics technique that is specifically directed toward single-cell studies. “[Electroporation for Single-Cell Analysis](#)” introduces advanced single cell electroporation techniques for cellular delivery and analysis, which might be potentially applicable to cell therapy, clinical diagnosis, drug screening, etc. “[Microinjection for Single-Cell Analysis](#)” is devoted to the single cell microinjection technique. The basic knowledge of this technique, its advantages and disadvantages, its development and applications, its basic instrumentation, and modifications are discussed thoroughly in this chapter. “[Optical Tools for Single-Cell Manipulation and Analysis](#)” demonstrates the optical tools for single-cell analysis ranging from optical trapping systems which provide a contact-free technique for manipulation of micron-scale objects, through to a selection of different optically-mediated cell membrane disruption methods available for lysis and/or delivery of material. “[Optoelectrokinetic Manipulation for Cell Analysis](#)” explores two newly developed optoelectrokinetic techniques termed rapid

electrokinetic patterning (REP) and optoelectronic tweezers (OETs). Both the fundamental knowledge and their applications in cell-related research are covered in this chapter. “[Continuous Micro-/Nanofluidic Devices for Single-Cell Analysis](#)” discusses continuous micro/nanofluidic devices for single-cell analysis in two parts. The first part presents state-of-the-art techniques developed to handle single cells, including counting, sorting, positioning, and culturing. The second part describes the manipulation techniques combined with other stimulating and sensing techniques for the observation and characterization of single cells. “[Single-Cell Mechanical Properties: Label-Free Biomarkers for Cell Status Evaluation](#)” emphasizes the microfluidic approaches including microfluidic constriction channels, microfluidic optical stretchers, and microfluidic hydrodynamic stretchers, which are being developed as next-generation, automated, and high-throughput techniques for characterization of the mechanical properties of single cells. “[Cytometry of Single-Cells for Biology and Biomedicine](#)” presents flow cytometry, scanning image cytometry, and microfluidic cytometry with fluorescent probes used for single-cell analysis in biology and biomedicine. It also discusses the advantages of combining different approaches in integrated instruments that could perform both flow cytometry and image analysis on single cells as well as examining the internal contents of each single cell. “[Single-Cell Genomics and Epigenomics](#)” discusses the role of single-cell analysis in genomics and epigenomics, where it describes the major technological developments achieved in single cell “omics,” the technical challenges to overcome, the potential applications, as well as future developments and breakthroughs. “[Single-Cell Metabolomics](#)” focuses on the single cell metabolomics in systems biology, where the recent improvement of analytical tools to unravel single cell metabolomics and their specificity, the limitations and challenges alongside the future prospects are discussed. “[Applications of Cell-Based Drug Delivery Systems: Use of Single Cell Assay](#)” presents different types of cell-based drug delivery systems to facilitate treatments for infectious and noninfectious diseases. Potential and limitations of single cell assay in this type of drug delivery systems is reviewed along with the clinical aspects. “[Applications of Single Cell Sequencing in Cancer](#)” describes the methodologies of single cell sequencing, as well as its existing and potential applications in reconstructing the evolutionary history of cancer progression and in profiling cancer transcriptome. “[Single-Cell Characterization of Microalgal Lipid Contents with Confocal Raman Microscopy](#)” highlights the recent advances in confocal Raman microscopy and its application in single cell characterization of microalgal lipid contents, which demonstrates cell-to-cell variation in structural features of expressed lipids among the screened *C. reinhardtii* mutants. “[Single Differentiated Neurons from Pluripotent Embryonic Stem Cells: Motor Protein Modeling and Neurodegenerative Disease](#)” illustrates how cross-field techniques, including the use of P19 neurons, single-cell DNA delivery devices, microchannel platforms, and kymograph data analysis for physical modeling, can enable the characterization of fundamental properties of neurodegenerative disease mechanisms.

We hope this book can be enjoyable reading material and at the same time a useful resource for scientists in academia and professionals in industry working on different aspects of SCA.

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Essentials of Single-Cell Analysis

Concepts, Applications and Future Prospects

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