BIOMEDICAL OPTICAL PHASE MICROSCOPY AND NANOSCOPY

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Preface

Living biological specimens, such as cells, tissues, or microorganisms, are microscopic dynamic objects, continuously responding to their environments and performing multiple processes by adjusting their three-dimensional sizes, shapes, and other biophysical features. Microscopy and nanoscopy of living specimens can provide a powerful tool for basic biological and biophysical studies, and for medical diagnosis and monitoring of disease progression.

Many living biological specimens such as cells in-vitro are transparent objects, and imaging them with conventional bright-field light microscopy fails to provide adequate contrast in the microscope image. For this reason, exogenous contrast agents such as fluorescent labels are widely used in biomedical microscopy. However, these exogenous agents are often cytotoxic and may influence the specimen behavior, especially in the long run. Additionally, fluorescent agents tend to photobleach which might limit imaging time and make signal quantification difficult.

Phase microscopy proposes a unique solution to the contrast problem. Phase is proportional to optical path delays of the light passing through the sample, and thus it captures information on the specimen structure and dynamics without using exogenous labeling.

This book presents a cutting-edge review of a variety of phase microscopy and nanoscopy techniques with emphasis on biomedical and clinical applications. The authors of each chapter are internationally renowned scientists, either phase microscopy and nanoscopy technology experts, or researchers who are interested in the biological and medical applications of these technologies. Based on this heterogeneous nature of the contributing authors, this book will not only be useful for researchers in the areas of biomedical engineering, electro-optics engineering, and nanotechnology engineering, but can also help biologists and clinicians who are interested in understanding the underlying principles and in learning about new biological and medical applications of conventional and novel phase microscopy methods.

As editors, we have invested efforts to order the book as a whole and the structure of each chapter in such as a way that the book is self-contained, with introductory subjects, followed by specific biomedical applications. Therefore, we expect that this book will be

useful for researchers at all levels including advanced undergraduate students, graduate students, postdoctoral fellows, and established researchers.

The book is divided into four parts based on the historical order of the technology inventions, starting with the older and widely-used technologies and finishing with the newer ones. The four part of the books are: Phase Contrast Microscopy and Differential Interference Contrast (DIC) Microscopy, Digital Holographic Phase Microscopy, Advanced Interferometric and Polarization Techniques, and Phase Nanoscopy. The first chapters in each of the four parts of the book contain an introduction to the relevant basic optical principles, followed by more advanced chapters that describe state-of-the-art advances and new applications.

Part 1 of this book deals with conventional and widely used phase microscopy methods: phase contrast and DIC microscopy. Chapter 1 introduces the basic principles of phase contrast microscopy, the first phase microscopy method, proposed by Zernike in the third decade of the nineteenth century, an invention that gained him the Nobel Prize in Physics in 1953. The typical artifacts of this technique and some common applications are also reviewed in this chapter. Chapter 2 presents another widely used phase microscopy technique: DIC microscopy, invented by Francis H. Smith in 1947. Chapter 3 describes a practical method that is based on phase contrast microscopy for conducting long-term time-lapse observations of living cells. Chapter 4 reviews phase imaging methods for plant cells and tissues.

Part 2 of this book introduces quantitative phase microscopy performed by digital holographic microscopy (DHM). Chapter 5 explains the principles of DHM used for measuring the quantitative phase maps and their interpretation for the calculation of biophysical parameters of biological cells. Chapter 6 presents new DHM setups and various applications. Chapter 7 focuses on the problem of 2π ambiguities in the quantitative phase profile and the possible solutions. Chapter 8 presents compact and portable phase microscopic designs and demonstrates the analysis of living sperm. Chapter 9 focuses on super-resolution methods using synthetic aperture for a simplified lensless DHM setup, which is used as examining tools for red blood cells and sperm cells. Chapter 10 presents the application of DHM for analyzing particles or live cells in microfluidic devices. Finally, Chapter 11 presents low-coherence DHM-based methods for tracing the internal motion in live cells and tissues, and demonstrates its applications for mapping functional motion in tumors and assessing drug effects.

Part 3 of this book focuses on advanced polarization and interferometric methods of phase microscopy, which are based on DHM introduced in Part 2 of this book, polarization microscopy, or a combination of both. Chapter 12 presents the tomographic phase microscopy technique in which the sample phase is captured using multi-viewpoint interferometric method, and then the data are processed into the three-dimensional map of the refractive index of the sample. Several demonstrations of cell imaging are presented. Chapter 13 discusses the phase-sensitive optical coherence tomography (OCT), an

interferometric method for measuring the quantitative phase for a single-point or a line of points on the sample, and several possible applications. Chapter 14 presents various advanced interferometric and DIC methods that use polarized light to capture the phase of the sample. Finally, Chapter 15 presents the polarization microscopy, a label-free technique that exploits the inherent birefringence in living cells to visualize dynamics of cell organelles.

Last but not the least, Part 4 of this book introduces phase nanoscopy used to visualize nanoscale objects. Chapter 16 discusses the idea of breaking the spatial resolution limit in phase microscopy, including definitions of the theoretical limit of resolution. Chapter 17 presents a method for combining total internal reflection (TIR) and DHM for visualizing nanoscale objects. Finally, Chapter 18 presents a unique nanoscopy approach that is based on interferometric imaging of fluorescence molecules using self-interference.

We strongly believe that phase microscopy and nanoscopy in the fields of biomedical, electro-optical and nanotechnology engineering will continue to develop rapidly and become one of the most important and widely used tools in biology and medicine, while offering unique opportunities for new and exciting applications. We hope that this book will contribute to the development of the field by providing a balanced and self-contained presentation of the field from different perspectives.

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