

Chapter XXXVII

Interference Microscopy for Cellular Studies

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ABSTRACT

This chapter describes the application of interference microscopy and double-wavelet analysis to non-invasive study of cell structure and function. We present different techniques of phase and interference microscopy and discuss how variations in the intrinsic optical properties of a cell can be related to the intracellular processes. Particular emphasis is given to the newly developed phase modulation laser interference microscope. We show how this setup, combined with wavelet analysis of the obtained data series, can be applied to live cell imaging to investigate the rhythmic intracellular processes and their mutual interactions. We hope that the discussion will contribute to the understanding and learning of new methods for non-invasive investigation of intracellular processes.

INTRODUCTION

There is a significant and rapidly growing interest in the development of new experimental techniques that will allow us to perform non-invasive studies on live cells with a spatial and temporal resolution

that is sufficient to reveal the motion of intracellular structures and to simultaneously follow cellular processes that take place in different compartments and on different time scales.

Most cells are practically transparent to light and limited information is directly available from conventional amplitude microscopy. To examine processes within the cell various forms of staining have to be used. However, such dye-based approaches only allow the investigation of a few processes at a time and, moreover, the staining affects normal cellular processes.

Local refractive index, an intrinsic optical property of biological objects, provides additional valuable information. Although a cell often doesn't absorb light efficiently, various cellular structures may have different values of the refractive index and therefore retard light beams that propagate through the object differently. The idea of exploiting the associated phase shifts underlies a number of different microscopy setups. A main advantage of the phase imaging technique is that no staining is required to visualize the transparent structures in the cell. Moreover, phase imaging allows the spatial resolution to exceed the Rayleigh barrier which is impossible in amplitude microscopy. Besides techniques for imaging it is also essential to develop non-invasive techniques that can be used to examine the dynamics of the cellular processes and their mutual interactions.

The possibility of using the intrinsic optical properties as a non-invasive probe of neuronal properties was first considered by Hill and Keynes (Hill and Keynes, 1968). They observed changes in the light scattering intensity of a nerve fibre during electrical activity. Cohen (Cohen, 1969) found that the intrinsic optical properties depend on the ion currents through the plasma membrane, and Stepnoski (Stepnoski et al., 1991) observed that the intensity of light scattered by neurons depends on their membrane potential. By now it is clear that the intrinsic optical properties of a cell also depend on the organization of the cytoskeleton and on the location of the various organelles (Haller, 2001). Cells exhibit dynamic processes over a broad range of different time scales and across a variety of cellular compartments. Moreover, these processes interact with one another to produce mutual modulation. It appears worthwhile to examine the possibility of time-resolved phase measurement for non-invasive studies of cellular processes. Such studies must, of course, be accompanied by a development of new mathematical methods capable of unravelling the complexity of the interacting processes.

The following section presents a general background for our discussion, describing a number of different approaches to phase imaging and providing an introduction to the use of wavelet analysis of rhythmic phenomena in non-stationary time series. This is followed by a section on cell visualization where we examine several cell types in order to clarify the kinds of information that one can obtain in such studies. Finally, we present the results of a time-resolved interference microscopy study of several cell types.

GENERAL BACKGROUND

Phase Microscopies

Phase Contrast

Historically, the first technique applied to convert phase shifts in the light passing through a transparent specimen into amplitude or contrast changes was phase contrast microscopy. This technique was invented by Frits Zernike in 1930s, and in 1953 he received the Nobel prize in physics for this invention.

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