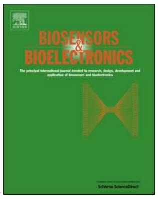
Biosensors and Bioelectronics ∎ (∎∎∎∎) ∎∎∎–∎∎∎

Contents lists available at ScienceDirect

Biosensors and Bioelectronics

journal homepage: www.elsevier.com/locate/bios



A review of recent progress in lens-free imaging and sensing

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ARTICLE INFO

Article history:
Received 7 June 2016
Received in revised form
27 July 2016
Accepted 31 July 2016

Keywords:
Lens-free imaging and sensing
From theory to applications
Shadow images
Diffraction patterns
CMOS image sensor

ABSTRACT

Recently, lens-free imaging has evolved as an alternative imaging technology. The key advantages of this technology, including simplicity, compactness, low cost, and flexibility of integration with other components, have facilitated the realization of many innovative applications, especially, in the fields of the on-chip lens-free imaging and sensing. In this review, we discuss the development of lens-free imaging, from theory to applications. This article includes the working principle of lens-free digital inline holography (DIH) with coherent and semi coherent light, on-chip lens-free fluorescence imaging and sensing, lens-free on-chip tomography, lens-free on-chip gigapixel nanoscopy, detection of nanoparticles using on-chip microscopy, wide field microscopy, and lens-free shadow image based point-of-care systems. Additionally, this review also discusses the lens-free fluorescent imaging and its dependence on structure and optical design, the advantage of using the compact lens-free driven equilibrium Fourier transform (DEFT) resolved imaging technique for on-chip tomography, the pixel super-resolved algorithm for gigapixel imaging, and the lens-free technology for point-of-care applications. All these low-cost, compact, and fast-processing lens-free imaging and sensing techniques may play a crucial role especially in the fields of environmental, pharmaceutical, biological, and clinical applications of the resource-limited settings.

1. Introduction

In recent years, the biomedical electronics industry has undergone a remarkable evolution, bringing compact and low-cost wearable devices to consumers. This evolution also triggered the development of various advanced sensing and characterization systems not just for academic research, but also for industries. The advances in computers, such as high-performance graphics processing units (GPUs) and central processing units (CPUs), facilitated the implementation of computational methods for fast characterization and prediction, thus decreasing their complexity and dependence on complex hardware components. This advancement in computational resources provided an opportunity to develop advanced biomedical imaging techniques such as computational tomography (CT) and X-ray imaging (Coskun and Ozcan, 2014). In addition, considerable effort using these advanced electronics and computational methods has gone into developing portable point-of-care devices. The design and development of a point-of-care diagnostic instrument that can improve the delivery of health care in resource-limited countries has been an ambitious goal. Such an instrument will improve health care by reducing the overall cost of testing and providing early diagnosis. The recent development of miniaturization technology such as 20-nm feature size fabrication and nano electromechanical systems (NEMS) has fueled research in and development of compact and integrated devices with very small form factors that are used on these kinds of diagnosis devices. These developments in semiconductor engineering lead to the compact and integrated optoelectronic products, including complementary metal oxide semiconductor (CMOS) and charge-coupled device (CCD) sensors, for use in imaging. These high-resolution sensors, along with the traditional optical components such as lenses, can acquire high-resolution microscopic images (Kim et al., 2012). However, the optical components are large and expensive, which in turn makes the whole system bulky and costly. Interestingly, due to the high pixel resolution, the image sensors can acquire diffraction patterns of microsamples without the use of any lenses (Gurkan et al., 2011). Recently, some research groups have tried to take advantage of these high-resolution sensors to fabricate a compact and lensless microscope (Kim et al., 2011). Significant progress has been made to achieve alternative imaging by integrating lens-free technology with the advances in computational and image-processing algorithms (Gorocs and Ozcan, 2013). The components used for this

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http://dx.doi.org/10.1016/j.bios.2016.07.115
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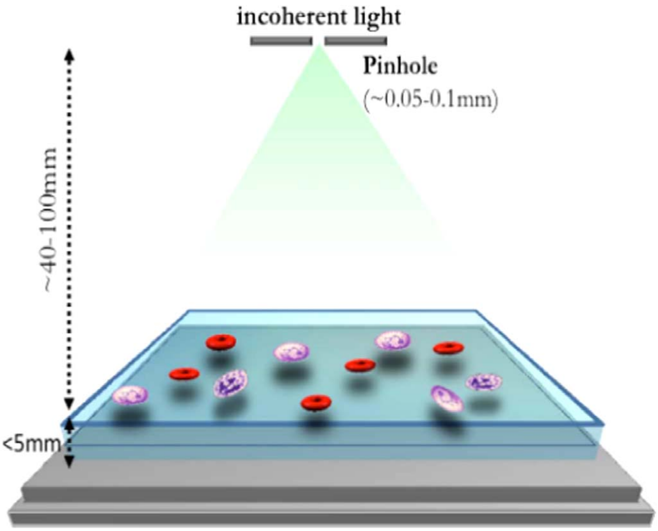

Fig. 1. Schematic of a lens-free imaging system showing the simplicity of the platform (Gorocs and Ozcan, 2013).

purpose, such as light-emitting diodes (LEDs) and CMOS image sensors, are low cost, lightweight, and easy to integrate (see Fig. 1), which makes the system simple. Several groups are working to develop various applications that take advantage of the lens-free imaging platform (Zhu et al., 2013a, 2013b). In this article, we discuss the development of lens-free imaging technology and its various applications.

2. Theory behind lens-free imaging and sensing

The basic principle of lens-free imaging can be explained using digital inline holography (DIH), a two-step process in which the amplitude and phase information of the wave front that originates from the object are digitally recorded and then reconstructed using computational algorithms (Gorocs et al., 2013). Digital inline holography became popular during the 1990s (Picart and Leval, 2008). Since then, its importance in applications because of its ability to image transparent objects and analyze images easily through mathematical morphology has been demonstrated.

In DIH, the hologram of an object is formed by a spherical wave of illumination of wavelength λ emitted from a point source about the size of the wavelength. This spherical wave splits into a scattered wave and an unscattered reference wave when it encounters an object (Fig. 2), creating interference patterns (hologram). This event can be expressed as $A_{\mathrm{scatr}}(r)=A(r)–A_{\mathrm{ref}}(r)$, where $A(r)$ is the amplitude of the incident wave, $A_{\mathrm{scatr}}(r)$ is the amplitude of the scattered wave, and $A_{\mathrm{ref}}(r)$ is the amplitude of the unscattered reference wave. Thus, the contrast of the hologram is defined as

$$I(r)=\left|A_{\mathrm{ref}}(r)+A_{\mathrm{scatr}}(r)\right|^2-\left|A_{\mathrm{ref}}(r)\right|^2 \tag{1}$$

$$I(r)=\left[A^*_{\mathrm{ref}}(r)A_{\mathrm{scatr}}(r)+A_{\mathrm{ref}}(r)A^*_{\mathrm{scatr}}(r)\right]-\left|A_{\mathrm{scatr}}(r)\right|^2 \tag{2}$$

The first term in Eq. (2), $\left[A^*_{\mathrm{ref}}(r)A_{\mathrm{scatr}}(r)+A_{\mathrm{ref}}(r)A^*_{\mathrm{scatr}}(r)\right]$, is the holographic diffraction pattern generated by the superposition of the reference wave directly from the source on the scattered wave from the object, and $\left|A_{\mathrm{scatr}}(r)\right|^2$ is the classical diffraction pattern generated by the interference of the scattered wave only (Xu et al., 2002). Because a hologram results from the interference between scattered and reference waves, the hologram of a transparent object can be created with DIH.

In general, the phase and amplitude data of the hologram are

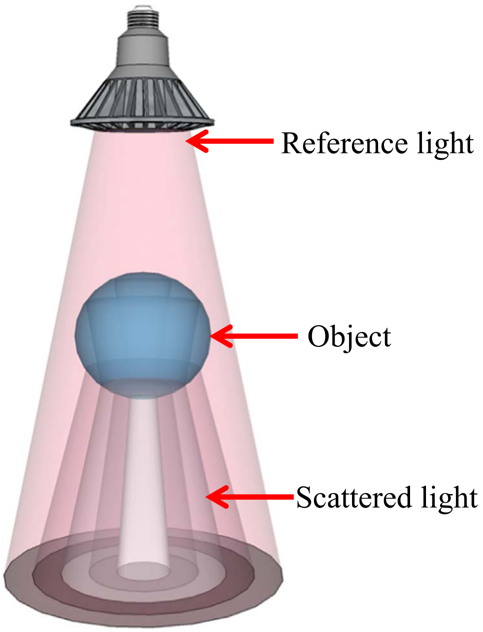

Fig. 2. Schematic of DIH. A coherent wave from a point source strikes an object and forms a scattered wave, which, in turn, forms a diffraction pattern of the object because of interference with the reference light.

recorded digitally by image sensors such as CMOSs or CCDs. These data are used in the numerical reconstruction process with the help of a computational algorithm. Reconstruction consists of virtually illuminating the recorded holographic pattern with a reference wave and evaluating the complex field distribution. The first DIH reconstruction was reported by Goodman and Lawrence in 1967 (Gorocs and Ozcan, 2013). However, the true revolution in holography began with the use of modern digital imaging sensors (i.e., CCDs and CMOSs) by Schnars and Jüptner (1994). In general, most current numerical reconstruction methods are based on the famous Kirchhoff–Helmholtz transform, which can be described by the following equation:

$$K(r)=\int_s \mathrm{d}s I(\xi)\exp(2\pi i\xi\bullet r/\lambda\xi) \tag{3}$$

where $\xi(x,y,L)$ is the 3D coordinate, L is the distance of the X,Y screen from the source, and $I(\xi)$ is the contrast of the hologram. This integration yields the reconstructed information of the object. Plotting $|K(r)|$ in an X,Y plane yields the 2D holographic reconstructed image, and stacking the 2D hologram yields the 3D information. The detailed steps of DIH are illustrated in Fig. 3.

Although the reconstruction provides high-precision surface topography of objects, artifacts associated with the acquisition process, such as twin images due to the zero-order term and complex conjugates of the object wave, make the reconstruction process a challenging one because the image sensor measures only the intensity profile of these waves. However, these kinds of artifacts can be eliminated with phase retrieval algorithms, but they make the system complex and place more demand on computational resources. This is useful for applications in which high-contrast topography of an object is required. Fortunately, common biological applications such as gathering information on the concentration or population of cells, determining cell size, and differentiating cell types do not require high-contrast topography. Therefore, research on lens-free shadow imaging with partially coherent planar wave illumination is ongoing. In this method, the sample-to-sensor distance is smaller than the source-to-sample distance. Fig. 4 presents a schematic of this approach. Because of this distance relationship, the reference wave can be considered a

Please cite this article as: Roy, M., et al., Biosensors and Bioelectronics (2016), http://dx.doi.org/10.1016/j.bios.2016.07.115