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Review Article

Sensitivity of photoacoustic microscopy

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ABSTRACT

Building on its high spatial resolution, deep penetration depth and excellent image contrast, 3D photoacoustic microscopy (PAM) has grown tremendously since its first publication in 2005. Integrating optical excitation and acoustic detection, PAM has broken through both the optical diffusion and optical diffraction limits. PAM has 100% relative sensitivity to optical absorption (i.e., a given percentage change in the optical absorption coefficient yields the same percentage change in the photoacoustic amplitude), and its ultimate detection sensitivity is limited only by thermal noise. Focusing on the engineering aspects of PAM, this Review discusses the detection sensitivity of PAM, compares the detection efficiency of different PAM designs, and summarizes the imaging performance of various endogenous and exogenous contrast agents. It then describes representative PAM applications with high detection sensitivity, and outlines paths to further improvement.

Contents

1. Introduction

In the last decade, photoacoustic tomography (PAT) has been drawing increasing attention from various research communities, including imaging, chemistry, material, physics, and biomedicine [1–3]. Briefly, in PAT, as photons travel in tissue, some of them are

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absorbed by molecules and their energy is partially or completely converted into heat. The heat then induces an initial pressure rise, which propagates as an acoustic wave. An ultrasonic transducer or transducer array detects the acoustic wave to form an image, which maps the original optical energy deposition in the tissue [4].

As shown in Fig. 1, PAT can be classified according to system attributes. These attributes include the image formation method, spatial resolution, number of ultrasonic transducer elements, image contrast, probe size, and image dimensions. For example, PAT has two major implementations based on their image formation methods [5]: reconstruction-based photoacoustic computed tomography (PACT), and acoustic-lens-based photoacoustic imaging. In PACT, the object is excited by a broadened laser beam. Ultrasonic transducers are placed around the object to simultaneously receive the ultrasonic waves emitted. At any given time point, an ultrasonic transducer integrates initial photoacoustic pressures over a spherical surface centered at the detector with a radius equal to the product of the speed of sound and the time. This integration is referred to as the spherical Radon transform. The spherical Radon transform can then be inverted by various reconstruction methods [6], such as the universal back-projection method [7] and iteration-based time reversal method [8], to map the laser-induced initial pressure rise distribution, which reflects the optical absorption contrast in the object.

Instead of reconstructing an image digitally in PACT, a focused ultrasound transducer is used for analog image reconstruction, most commonly, in photoacoustic microscopy (PAM). Upon a pulsed laser excitation, the focused ultrasound transducer picks up a time-resolved PA signal emitted from the acoustic focal zone. A single laser pulse yields a 1D image. Scanning across the tissue yields a 2D image. Raster scanning yields a 3D image. The acoustic focusing can be accomplished either by affixing an acoustic lens (spherical or cylindrical) to a flat ultrasonic transducer or by curving the active ultrasonic element itself. Here, we define PAM as an implementation of PAT with a spatial resolution finer than 50 μm, since the naked eye can discern features larger than 50 μm. By using a 5 MHz focused ultrasonic transducer, deep-penetration photoacoustic macroscopy (PAMac) relaxes the lateral resolution to 560 μm and extends the maximum imaging depth to a few centimeters. PAMac is not classified as microscopy but is covered in this Review to demonstrate the scalability of PAT. In addition, photoacoustic endoscopy (PAE) is considered as a variant of PAM for internal organ imaging, which is typically rotational scanning based.

Harnessing the rich optical absorption contrast and the low ultrasonic scattering in tissue, PAT is one of the fastest growing biomedical imaging modalities [1]. Comprehensive reviews of PAT technology can be found in previous publications [3,9]. Here, we will focus only on the development of PAM technology. PAM typically employs raster-scanning of its optical and acoustic foci and forms images directly from acquired depth-resolved signals [10]. While the axial resolution of PAM is primarily determined by the imaging depth and the frequency response of the ultrasonic transducer, its lateral resolution is determined by the product of the point spread functions of the dual foci. Based on its configuration, PAM can be further classified into optical-resolution PAM (OR-PAM), where the optical focus is much smaller than acoustic focus [11], and acoustic-resolution PAM (AR-PAM), where the acoustic focusing is tighter [12,13].

Among all the imaging parameters of PAM, detection sensitivity is of particular interest, since it reflects the minimum number of targets at different length scales (e.g., melanoma tumor cells, hepatitis virus, glioblastoma-targeting nanoparticles and hemoglobin molecules) needed to measure signals above the noise and provide accurate diagnosis of disease [10,14–17]. For example, in early cancer detection, it is required that PAM should be able to detect as few as 10^4 cancer cells (0.01 mg or 0.01 mL), because malignant switching in cancer progression typically needs $\sim 10^5$ cells growing as a single mass [18]. In PAM, energy is transformed through three steps. First, optical (electromagnetic) energy is

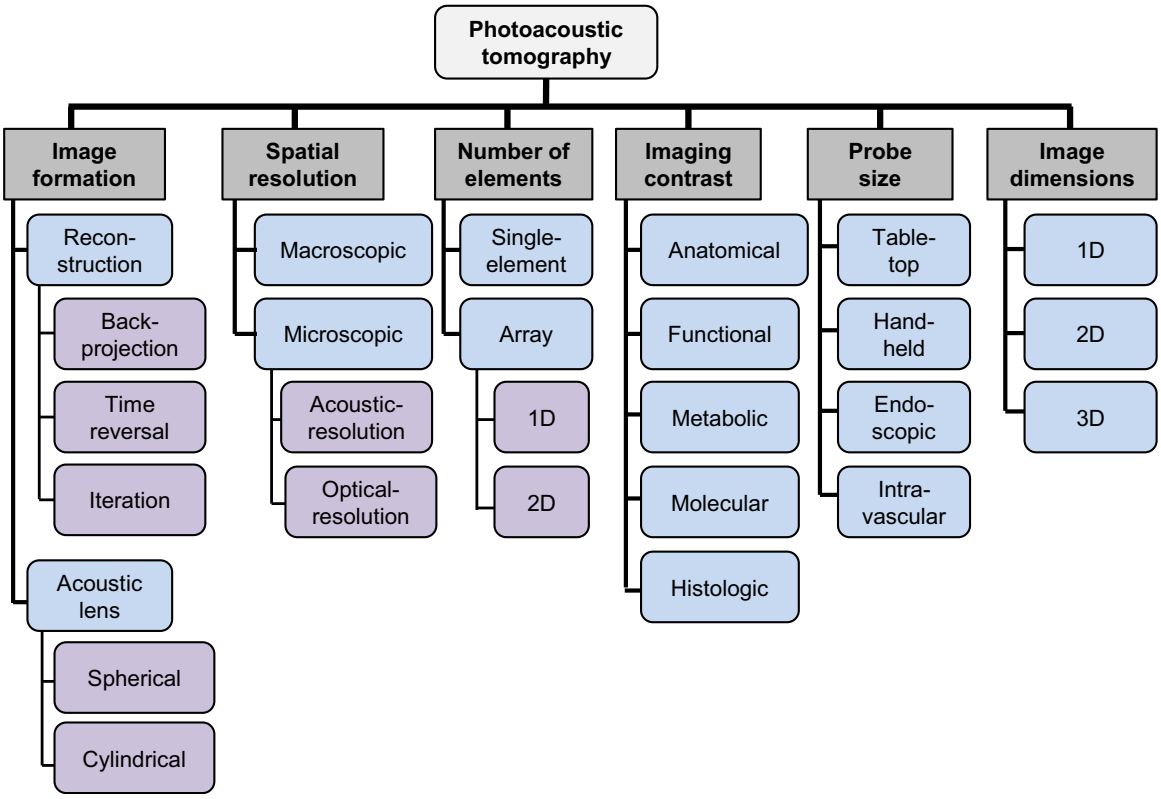

Fig. 1. Classification of photoacoustic tomography based on different system attributes.