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Review article

Review of photoacoustic flow imaging: its current state and its promises

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ABSTRACT

Flow imaging is an important method for quantification in many medical imaging modalities, with applications ranging from estimating wall shear rate to detecting angiogenesis. Modalities like ultrasound and optical coherence tomography both offer flow imaging capabilities, but suffer from low contrast to red blood cells and are sensitive to clutter artefacts. Photoacoustic imaging (PAI) is a relatively new field, with a recent interest in flow imaging. The recent enthusiasm for PA flow imaging is due to its intrinsic contrast to haemoglobin, which offers a new spin on existing methods of flow imaging, and some unique approaches in addition. This review article will delve into the research on photoacoustic flow imaging, explain the principles behind the many techniques and comment on their individual advantages and disadvantages.

Contents

1. Introduction . . . 89
1.1. Current modalities . . . 90
1.2. The case for PA flow imaging . . . 90
2. Photoacoustic flow imaging methods . . . 91
2.1. Doppler shift . . . 91
2.1.1. Continuous-wave photoacoustic Doppler . . . 91
2.1.2. Structured-illumination photoacoustic Doppler . . . 91
2.2. Density tracking . . . 93
2.2.1. Cross-correlation flow imaging in the time domain . . . 93
2.2.2. Cross-correlation flow imaging in the spatial domain . . . 93
2.3. Transit time . . . 94
2.3.1. Transit-time flow imaging of single-particles . . . 94
2.3.2. Transit-time flow imaging of particle ensembles . . . 94
2.4. Amplitude encoding . . . 96
2.4.1. Photoconversion and replenishment . . . 96
2.4.2. Heat encoding and convection . . . 96
2.5. Discussion and conclusion . . . 98
Acknowledgements . . . 98
References . . . 98

1. Introduction

Blood flow in arteries, veins and smaller capillaries is an important aspect in the diagnosis of a wide range of pathologies and diseases.

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Blood flow can be estimated with either flow imaging or perfusion imaging, and both provide distinct and valuable information. Flow imaging is the process of mapping where functional vascularity is, or what the flow profile is within an artery or vein. The latter can be used for estimating, for example, the wall shear rate [1] or detecting where turbulent blood flow occurs [2,3]. Imaging vascularity is important to reveal for example angiogenesis [4], the process during which rapid growth of new vasculature occurs. The resulting vasculature, irregularly and haphazardly shaped, is the pathological result of for instance tumour growth [5] and inflammatory diseases such as rheumatoid arthritis [6].

Perfusion imaging is related to flow imaging, but provides a more global picture of vascularity, that describes how much blood reaches organs, muscles or skin over time [7]. The amount of skin perfusion determines for instance the chance of a burn healing [8], and in cerebral ischemia, malperfusion of parts of the brain leads potentially to stroke [9]. The perfusion can be visualised as the integration of flow speed over the total cross sectional area of the feeding vasculature [10]. Perfusion and the amount of flow imaged are therefore closely related in some clinical applications, however, computing the perfusion from imaged vascularity is often challenging [11].

Photoacoustic imaging has the potential to do both: perfusion imaging and flow imaging. In this review we will only focus on the latter. A wide variety of methods investigated by different research groups, inspired by other imaging modalities, in addition to a few approaches that utilise unique aspects of photoacoustic imaging, make the review a worthwhile investigation. We will first briefly discuss existing imaging modalities that are capable of both perfusion imaging and flow imaging before describing the different photoacoustic approaches developed so far.

1.1. Current modalities

Magnetic resonance imaging (MRI) is a widely used modality for imaging perfusion and flow, using a range of methods [12,13]. For instance, imaging flow can be performed using phase contrast MRI [14], while perfusion imaging can be done with arterial spin labelling [15] or dynamic contrast enhanced imaging [16]. MRI can provide blood flow information of the whole body, with high sensitivity and resolution [17], which makes it unique in that aspect. Moreover, it can be combined with blood-oxygenation-level dependent (BOLD) MRI [18]. However, MRI is very expensive in both the initial investment and the upkeep, and the extensive pulsing schemes in MRI also make imaging a slow process [19].

Dynamic contrast enhanced computed tomography (CT) is a more affordable modality for perfusion imaging, unlike MRI. It can also be combined with positron emission tomography (PET) for quantification of e.g. glucose consumption for estimation of the complete metabolic activity [20]. Like MRI, CT is also capable of imaging complete organs or even the whole body, but with worse resolution and it relies on ionizing radiation, making it unpractical for monitoring [19].

Ultrasound (US) imaging is another widely used technique for both flow and perfusion imaging. Over several decades, the ultrasound community has developed many techniques. For instance, flow imaging can be performed using continuous wave excitation in spectral Doppler US [21], by imaging phase change of reflected US pulses in colour flow imaging [22] or by transverse speckle tracking [23]. Perfusion imaging is performed using dynamic contrast enhanced US, for example by using a flash-replenishment technique [24]. US imaging is very scalable through the inverse relationship of penetration depth and resolution, which can be tuned using the ultrasound emission frequency and bandwidth [25]. Furthermore, US imaging is both affordable and portable [26]. While imaging depth is larger than optical coherence tomography, the resolution is poorer and it suffers from clutter [27].

Several modalities are being developed to estimate flow and perfusion using visible or infrared light, which makes these techniques both harmless and affordable. For example, laser Doppler perfusion imaging (LDPI) and laser speckle imaging (LSI) are two modalities based on tracking diffusely reflected light over time and can be used for perfusion imaging of the skin [28], with the advantages of portability, low cost and real-time imaging [29,30]. On the other hand, LDPI and LSI are limited to superficial imaging and low resolution [28] and do not feature depth resolution. While LDPI has the objective underlying principle of velocity related Doppler shifts, quantifying perfusion in an absolute manner remains challenging in both LDPI and LSI because of the unknown optical properties of the tissue [31]. Another optical technique, orthogonal polarization spectral imaging (OPS), can be used for high-resolution imaging of micro-vasculature [32]. Resolution is high and penetration depth is fair, but flow quantification is very challenging.

Optical coherence tomography (OCT) is an optical technique which can be used for flow imaging as a function of depth [33]. Flow can be quantified, for instance, by tracking the phase change of the reflected light over time, or by computing the speckle variance [34]. OCT has high resolution, is depth resolved and can be portable, but suffers from limited penetration depth and is hindered by clutter [35].

In this regard PAI is comparable to fluorescence microscopy approaches like confocal microscopy [36] or the two-photon variant [37]. In both microscopy techniques flow imaging is performed by laser scanning along the flow direction. However, confocal and two-photon require fluorescent markers that are susceptible to photobleaching; are only useable in superficial applications; and the laser scanning makes it only suitable for imaging a few blood vessels at a time [38]. As we will see, photoacoustics can be used to overcome these problems in flow imaging. Photoacoustic flow imaging, uses endogenous contrast, and allows approaches not limited to specific targeting of blood vessels.

1.2. The case for PA flow imaging

Photoacoustic imaging (PAI) is an optical modality that relies on light pulses to generate ultrasound at locations of high optical absorption [39]. Nanosecond light pulses are directed onto the skin, where they diffuse through tissue, down to several centimetres for near-infrared light. The light is locally absorbed by tissue chromophores, and is converted into heat, causing a pressure build-up. This build-up is released in the form of pressure waves: sound waves very similar to those emitted in pulse-echo ultrasound.

The main tissue chromophores in the visible and near infrared wavelengths (NIR) are haemoglobin and melanin ($<$1000 nm); at NIR wavelengths ($>$930 nm) lipids also exhibit absorption peaks that can be utilized [40]. PAI can therefore be used spectroscopically and, using spectral unmixing, the relative concentrations of chromophores can be extracted [41]. In this way, the oxygenation of blood vessels can be determined by exploiting the oxygenation-dependent absorption spectrum of haemoglobin [42,43].

Like ultrasound imaging, PAI is relatively low cost, can be used in portable devices [44], and the resolution can be increased relatively easily though at the cost of imaging depth. PAI is used in microscopy, tomography and linear array systems, with varying resolutions and imaging depths [45]. An important distinction in systems can be made, namely between acoustic and optical resolution setups. In optical resolution mode, laser light is focussed onto a sample; in acoustic resolution mode, generated sound waves are focussed in detection with a large numerical aperture–either physically or in computed reconstruction. The focal size