Photoacoustics 1 (2013) 36–42

Contents lists available at ScienceDirect

Photoacoustics

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

Research Article

Optical wavelength selection for improved spectroscopic photoacoustic imaging

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ARTICLE INFO

Article history:
Received 19 May 2013
Received in revised form 23 July 2013
Accepted 1 August 2013

Keywords:
Spectroscopic photoacoustic imaging
Feature selection
Spectral unmixing
Spectroscopy

ABSTRACT

Spectroscopic photoacoustic imaging has the potential to become a powerful tool that can estimate distributions of optically absorbing chromophores in the body. We have developed an algorithm to select imaging wavelengths for spectroscopic photoacoustics given the spectra of expected chromophores. The algorithm uses the smallest singular value of a matrix constructed from the absorption spectra as a criterion to remove extraneous wavelengths. The method performed significantly better than an approach where evenly spaced wavelengths were used in the presence of noise and wavelength-dependent attenuation of light in tissue. Finally, the algorithm was applied to photoacoustic imaging of a phantom containing indocyanine green dye and silica-coated gold nanorods, demonstrating significant improvements in the ability to estimate relative contrast agent concentrations compared to the case where evenly spaced wavelengths were chosen. In summary, our work provides a versatile framework to select optical wavelengths and evaluate sets of absorbers for spectroscopic photoacoustic imaging.

1. Introduction

Photoacoustic (PA) imaging, also known as optoacoustic imaging, is a rapidly growing biomedical imaging modality [1–5]. PA imaging offers high contrast derived from differences in optical absorption with excellent resolution at clinically relevant depths. Endogenous chromophores, such as hemoglobin, melanin, and lipids, can all be detected using PA imaging [6–8]. This shows great promise for the noninvasive clinical detection and characterization of atherosclerotic plaques [9,10] and certain tumors [11]. Highly absorbing contrast agents (e.g., dyes or plasmonic nanoparticles) are commonly used in conjunction with PA imaging [12–16]. These contrast agents are often molecularly targeted to observe a specific cellular expression or interaction, allowing for further characterization of the disease [15,17].

The optical absorption spectra of the tissue components and contrast agents vary greatly with optical wavelength. Therefore, spectroscopic methods can be used to unmix the signals from different optical absorbers in a photoacoustic image and provide an estimate of their concentrations [8,13,18]. This technique is known as spectroscopic PA (sPA) imaging. sPA imaging allows for accurate measurement of blood oxygenation saturation (SO_2) or nanoparticle deposition in tissue [19,20].

A number of methods have been proposed to spectrally unmix absorbers in PA images. One simple spectroscopic method uses a ratio of the PA signals acquired at two optical wavelengths. This ratio is then used to estimate either SO_2 or the state of an activatable contrast agent [21,22]. The main drawback of using a ratio is that at most two absorbers can be distinguished, limiting the potential applications. Intraclass correlation (ICC) has been used to simultaneously identify multiple absorbers. ICC correlates the measured PA spectrum at each pixel to the known absorption spectra of the anticipated absorbers and assigns each pixel to one (and only one) absorber [13]. This method can identify multiple chromophores, but the assumption that each pixel only contains one absorber is not always valid – particularly in the case of blood, where the spectrum is a linear combination of deoxygenated and oxygenated hemoglobin, depending on the level of SO_2.

An alternative approach, which treats each pixel as a linear combination of absorbers, provides a more realistic model [20]. Thus, each pixel can contain multiple absorbers and the relative contribution of each absorber to the overall spectrum can be estimated. A linear model is then used to calculate the absorber concentrations in each pixel while minimzing the mean squared error.

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2213-5979
http://dx.doi.org/10.1016/j.pacs.2013.08.001

In each aforementioned method, the choice of optical wavelengths is critically important. The unique spectral features of each absorber must be captured by a discrete set of wavelengths. Ideally, a large number of wavelengths spanning a broad spectrum should be used. In practice, the number of wavelengths that can be used is limited by a number of factors, including the linewidth of the laser, the spectral range of the laser, the spectral-dependent attenuation of light in tissue, and the pulse repetition rate of the laser. In PA imaging, the temporal resolution is primarily limited by the pulse repetition rate of the laser, typically 10–20 Hz for a high energy tunable laser system. Each imaging wavelength further decreases the temporal resolution, thereby increasing the overall imaging time and the likelihood of introducing motion artifacts, which can be detrimental to spectral unmixing. Thus, wavelength selection can be used to improve the temporal resolution while maintaining acceptable levels of uncertainty in the estimated chromophore concentrations. Heretofore, the optical wavelengths used in sPA imaging have typically been chosen heuristically. Here we present a method to select optical wavelengths such that the concentration estimation remains robust in the presence of noise.

2. Theory

Assuming the stress and thermal confinements are met (i.e., the laser pulse length is short enough that the local pressure and temperature rise are constrained to a small volume), the peak pressure, P, generated by the PA effect depends on the Grüneisen parameter of the tissue, Γ, the laser fluence at the absorber, F, and the optical absorption coefficient of the absorber, μ_a [23]:

$$P = \Gamma F \mu_a \tag{1}$$

In practice, the pressure detected by an ultrasound transducer has been attenuated as the pressure wave travels through the tissue toward the transducer. Accurate reconstruction of P is not trivial and depends on the geometry and point spread function of the transducer [24]. In this paper, to simplify the problem and focus on spectral unmixing, we assume that P has been accurately reconstructed.

Additional factors also complicate Eq. (1). In practice, F can vary greatly depending on optical properties of tissue and optical wavelength, λ. Furthermore, μ_a is a function of λ and each of N distinct absorbers in the region of interest will contribute to the overall absorption. Thus, Eq. (1) becomes:

$$P(\lambda) = \Gamma F(\lambda)(\mu_{a_1}(\lambda) + \mu_{a_2}(\lambda) + \cdots + \mu_{a_N}(\lambda)). \tag{2}$$

The optical absorption can be related to the concentration of an absorber and the absorption cross section as follows:

$$\mu_{a_i}(\lambda) = C[i]\varepsilon_{a_i}(\lambda), \tag{3}$$

where $C[i]$ is the concentration of the ith absorber and $\varepsilon_{a_i}(\lambda)$ is the molar absorption cross section of the ith absorber at wavelength λ. Eq. (2) is then expanded to:

$$P(\lambda) = \Gamma F(\lambda)(C[1]\varepsilon_{a_1}(\lambda) + C[2]\varepsilon_{a_2}(\lambda) + \cdots + C[N]\varepsilon_{a_N}(\lambda)). \tag{4}$$

The Grüneisen parameter is tissue-dependent and has little variation in water-based tissues at constant temperature. Therefore, it is often assumed to be constant. If the fluence at the absorber is known, then the optical absorption coefficient vector, $\mu_{\text{est}}(\lambda)$, can be estimated:

$$\mu_{\text{est}}(\lambda) = \frac{P(\lambda)}{\Gamma F(\lambda)}. \tag{5}$$

Then Eq. (4) can be simplified to a set of linear equations:

$$\boldsymbol{\mu}_{\mathbf{est}} = \boldsymbol{\varepsilon}\mathbf{C}, \tag{6}$$

where $\boldsymbol{\mu}_{\mathbf{est}}$ is a vector whose components correspond to the reconstructed absorption coefficient at each individual optical wavelength, $\boldsymbol{\varepsilon}$ is the absorption cross-section matrix whose rows correspond to optical wavelengths and columns are the normalized absorption cross section spectra of the optical absorbers (i.e., $\varepsilon_{\mathbf{ij}} = \varepsilon_{a_j}(\lambda_i)$), and $\mathbf{C}$ is a vector whose elements correspond to the relative concentration of each optical absorber.

In order to solve Eq. (6) for the absorber concentrations, the number of optical wavelengths used to acquire images, M, must be greater than or equal to the number of absorbers, N. In the presence of noise, it is useful to have $M > N$, thus making Eq. (6) over-constrained. In this case, a least squared error estimate of $\mathbf{C}$ can be found:

$$\mathbf{C} \approx \varepsilon^{+}\boldsymbol{\mu}_{\mathbf{est}}, \tag{7}$$

where $\boldsymbol{\varepsilon}^{+}$ is the Moore-Penrose pseudoinverse of $\boldsymbol{\varepsilon}$, defined as [25]:

$$\varepsilon^{+} = (\varepsilon^{\mathrm{T}}\varepsilon)^{-1}\varepsilon^{\mathrm{T}}. \tag{8}$$

This estimate of the concentrations has been used to simultaneously measure SO_2 and the concentration of a dye or nanoparticles in vivo [19,20]. Further modifications can be made to Eq. (7) to ensure the sum of the concentrations is 1 and negative concentrations (an artifact related to finite signal-to-noise ratio of the images or the presence of an absorber not included in absorption cross-section matrix) are avoided [20,26].

3. Materials and methods

3.1. Wavelength selection algorithm

The goal of the wavelength selection algorithm was to select a set of optical wavelengths in such a way as to increase the accuracy of existing spectral unmixing algorithms. This set of imaging wavelengths was chosen from a larger set of wavelengths for which accurate values of $\mu_a(\lambda)$ for each of the absorbers in the imaging volume were found from literature or were measured (e.g., via spectrophotometry). Extraneous wavelengths were recursively discarded such that the salient features of each absorber's spectrum were maintained.

First, the molar absorption matrix, $\boldsymbol{\varepsilon}$, was populated with the absorption spectra with N columns corresponding to individual absorbers and M rows corresponding to the optical wavelengths. Only absorbers that are present in the imaging volume and generate detectable PA signal in the spectral range should be included in $\boldsymbol{\varepsilon}$. The number of rows is limited by a number of factors, including the spectral range of the laser and spectral resolution of the absorption spectra data. It was assumed that the rank($\boldsymbol{\varepsilon}$) = N. That is, the concentrations of all N absorbers can be perfectly reconstructed from the M wavelengths in the absence of noise.

The smallest singular value of $\boldsymbol{\varepsilon}$, $\sigma_{\min}$, was used as an indication of its stability. As $\sigma_{\min} \to 0$, $\boldsymbol{\varepsilon}$ becomes unstable and may lose rank in the presence of noise. In other words, the spectrum of one absorber can be approximated by a linear combination of the other absorbers. Thus, multiple combinations of absorber concentrations can represent a single PA spectrum.

Each row was iteratively removed from $\boldsymbol{\varepsilon}$ and $\sigma_{\min}$ was calculated for the truncated matrix. The row whose removal resulted in the largest $\sigma_{\min}$ was taken to correspond to the least-critical wavelength and was excluded. This process was recursively repeated until the desired number of wavelengths was reached. In practice, the number of wavelengths will depend on the temporal resolution required, the noise level of the imaging system, and the desired level of accuracy in concentration estimations. The implementation of the algorithm is outlined below: