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Research Article

Influence of nanoscale temperature rises on photoacoustic generation: Discrimination between optical absorbers based on thermal nonlinearity at high frequency

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ABSTRACT

In this work, we experimentally investigate thermal-based nonlinear photoacoustic generation as a mean to discriminate between different types of absorbing particles. The photoacoustic generation from solutions of dye molecules and gold nanospheres (same optical densities) was detected using a high frequency ultrasound transducer (20 MHz). Photoacoustic emission was observed with gold nanospheres at low fluence for an equilibrium temperature around 4 °C, where the linear photoacoustic effect in water vanishes, highlighting the nonlinear emission from the solution of nanospheres. The photoacoustic amplitude was also studied as a function of the equilibrium temperature from 2 °C to 20 °C. While the photoacoustic amplitude from the dye molecules vanished around 4 °C, the photoacoustic amplitude from the gold nanospheres remained significant over the whole temperature range. Our preliminary results suggest that in the context of high frequency photoacoustic imaging, nanoparticles may be discriminated from molecular absorbers based on nanoscale temperature rises.

1. Introduction

Photoacoustics has demonstrated optical contrast imaging in biological tissues at depth beyond 1 mm [1]. This non-invasive hybrid modality uses the conversion of transient illumination to ultrasound wave through thermoelastic expansion to detect optical absorption. Besides the detection of endogenous photoabsorbers such as hemoglobin and melanin, the use of exogenous contrast agents has been shown to provide functional and molecular information [2]. Optical reporter agents in photoacoustics range from molecular agents to nanoparticles. Organic dyes like ICG [3,4] and methylene blue [5] are of molecular agents and have already been used to enhance visualization of the circulatory system and its dynamics. Gold nanoparticles have been used in particular to image the enhanced permeability and retention effect in tumors [6] or their long term biodistribution in small animals [7]. Although relative variations of the amplitude of the photoacoustic signal could be sufficient if images are taken at different time points before and after the injection, multispectral approaches are usually employed to improve the specificity of the detection. The retrieval of spectral signatures of contrast agents can be challenging. Indeed, most of reconstruction algorithms [8,9] and analytical derivation of the photoacoustic signal [10] assume that the reconstructed initial pressure in the medium is directly proportional to the optical absorption and the fluence. However, because of the wavelength-dependent absorption of the excitation before reaching the region of interest, the relationship between the fluence on the sample surface and at the imaged position can be non-trivial. Specific detection by suppressing background signal has also been demonstrated using magnetic contrast agents for magnetomotive photoacoustic imaging [11].

In this work, we consider photoacoustic nonlinearity as a candidate mechanism to discriminate between various types of optical absorbers. Several phenomena may induce nonlinear relationships between the photoacoustic signal amplitude and the energy of the incident light, such as optical saturation [12,13], temperature-dependence of thermodynamic parameters [14–16], photo-chemical reaction [17], or nano/micro-bubble formation [18]. Nonlinear phenomena could be on their own a means of selectively detect contrast agents, similarly as what is done in the field of ultrasound imaging. In the context of biomedical imaging, exploiting photoacoustic nonlinearity has been reported in a few recent works. In [19,20], the authors used nonlinear amplification of photoacoustic signals from laser-induced nano-bubbles. However, laser-induced bubbles may involve potential damages to tissue, a potentially useful feature for therapeutic approach [21]

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but which may also limit the application of this approach for *in vivo* imaging. In the thermoelastic regime considered here in our work, a previous experimental study reported a nonlinear signal increase with the laser fluence, presumably caused by thermal coupling within aggregated nanoparticles in cells [22]. The main objective of this study is to demonstrate the ability to discriminate between different types of absorbers (dye molecules and gold nanospheres) based on thermal nonlinearity, i.e. in a regime that precludes phase transitions involved in bubble formation. We first give an introduction to the so-called thermal nonlinearity in photoacoustics and discuss some theoretical predictions. Experimental results are then qualitatively compared to theoretical predictions.

2. Theoretical background

2.1. Nonlinear photoacoustic generation in the thermoelastic regime

In a theoretical work published in 2001, Calasso et al. [15] analytically calculated a nonlinear contribution to the photoacoustic signal emitted by a point absorber. In this simplified model, the absorber immersed in a surrounding fluid was of vanishingly small size but with a finite optical absorption cross-section. As a consequence, the photoacoustic generation was dictated by the thermodynamics properties (speed of sound c_s, density ρ, specific heat capacity c_p and coefficient of thermal expansion β) of the mere fluid, in particular via its Grüneisen coefficient $\Gamma = (\beta c_s^2)/(c_p)$. Amongst the relevant thermodynamics properties, β shows the most significant temperature dependency, illustrated in Fig. 1. The nonlinearity predicted in [15] arose from the temperature-dependence of β in the photoacoustic wave equation [23,24]:

$$\left[\frac{1}{c_s^2}\frac{\partial^2}{\partial t^2} - \Delta\right] p(\mathbf{r},t) = \rho \frac{\partial}{\partial t}\left[\beta(T)\frac{\partial T}{\partial t}\right](\mathbf{r},t) \quad (1)$$

where $T(\mathbf{r}, t)$ is the temperature field in water. By linearizing the temperature-dependence of $\beta(T)$ around the equilibrium temperature in the medium, according to the following equation [23]

$$\beta(T) = \beta(T_{eq} + \delta T) = \beta_{eq} + \delta T \frac{d\beta}{dT}(T_{eq}) \quad (2)$$

Calasso et al. separately calculated two terms in the expression of the photoacoustic signal: a linear term corresponding to the photoacoustic emission assuming that β had not changed in response to the temperature rise induced by the optical absorption, and a nonlinear term attributed to the local temperature rise. This so-called thermal nonlinearity, earlier introduced in [14], results from the dynamic transient change of the coefficient of thermal expansion during the pulsed illumination. The nonlinear contribution may become significant only if temperature rises are high enough to affect the value of $\beta(T)$ during the illumination. For water, the linear contribution vanishes around $T_{eq} \sim 4$ °C, and therefore only the nonlinear contribution should remain, as has been experimentally observed from protons absorption experiments in water [25].

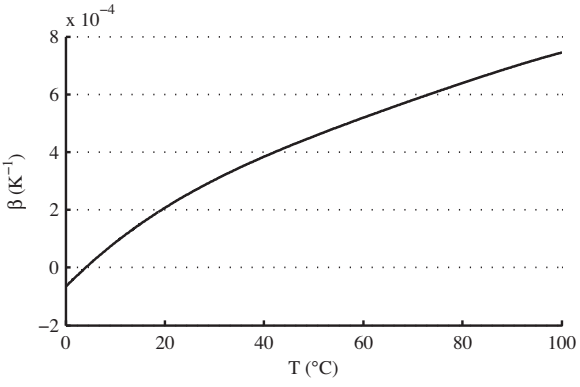

Fig. 1. Coefficient of thermal expansion of water β as a function of temperature [26]. Note that β vanishes for $T \sim 4$ °C.

In summary, thermal-based photoacoustic nonlinearity is expected to be significant in comparison to the linear contribution, and then accessible to experiments, either when the illumination fluence is large enough to induce a significant temperature rise, or when the equilibrium temperature approaches 4 °C so that the linear contribution becomes negligible as compared to the nonlinear one.

The objective of the current work is to address these qualitative predictions with experiments performed with two types of absorbers, a solution of dye molecules and a solution of gold nanospheres. The temperature rise around gold nanospheres in aqueous solution may become significant, due to the large absorption cross-section of gold nanoparticles and the partial heat confinement caused by the nanometric size. On the other hand, negligible local temperature rise will be encountered with a solution of dye molecules of equivalent optical density: in this case, light is absorbed by a much larger number of dye molecules with as much lower absorption cross-sections, resulting in a very weak temperature rise at the scale of each individual absorbers. Therefore, one expects the thermal nonlinearity to possibly manifest itself with solutions of gold nanoparticles, while solution of dye molecules of equivalent optical density are expected to behave linearly.

2.2. Prediction for gold nanospheres

Gold nanospheres with a diameter of a few tens of nanometers cannot be reduced to point absorbers [16]. On the other hand, it has recently been demonstrated experimentally that for nanosecond illumination, it is mostly the fluid surrounding the nanoparticles that emits photoacoustic waves [27]. From a theoretical point of view, the prediction of the photoacoustic wave emitted by a gold nanosphere requires to first solve the diffusion equation for the temperature field in the sphere and its environment, and then use this temperature field as a source term in the photoacoustic wave equation. Because the heat diffusion characteristic time for gold nanospheres is of the same order of magnitude as the illumination time, the problem is analytically intractable, even in the linear regime where β is assumed to be constant. Moreover, taking into account the temperature-dependence of $\beta(T)$ makes the problem even more difficult to solve by means of analytical methods. Calasso et al. could provide a solution only under the assumption of a point absorber and after linearization of the temperature dependence of $\beta(T)$ [15]. Taking into account the size of the absorber has been done in [16], but results could only be found for either thermally small or large absorbers, assumptions that do not hold for gold nanospheres. Numerical approaches are required to obtain accurate predictions of temperature rise and subsequent thermal-based photoacoustic nonlinearity. It is out of the scope in this experimental report to describe the numerical methods that can be used to solve both the thermal and the photoacoustic problems. Suffice it to say that theoretical predictions from a numerical resolution [23,24] are in qualitative agreement with the main prediction that can be drawn from the work by Calasso et al., namely that significant temperature rise around efficient optical absorbers yields a nonlinear relationship between the amplitude of photoacoustic signals and the light fluence. For nanoparticles, such nonlinearities have first been observed in the case of highly diluted suspension by Egerev and Oraevsky [28]. As already discussed