Research Article

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

Olivier Simandoux, Amaury Prost, Jérôme Gateau, Emmanuel Bossy*

ESPCI ParisTech, PSL Research University, CNRS, INSEBM, Université Pierre et Marie Curie, Institut Langevin, 1 rue Jussieu, 75005 Paris, France

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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.

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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 photo-absorbers 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].
but which may also limit the application of this approach for \textit{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 \( \rho \), specific heat capacity \( C_p \), and coefficient of thermal expansion \( \beta \)) of the fluid, in particular via its Grüneisen coefficient \( \Gamma = (\beta c_s^2)/(C_p) \). Amongst the relevant thermodynamics properties, \( \beta \) shows the most significant temperature dependences, illustrated in Fig. 1. The nonlinearity predicted in [15] arose from the temperature-dependence of \( \beta \) in the photoacoustic wave equation [23,24]:

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

(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]

\[
\beta(T) = \beta(T_{eq}) + \delta T \frac{d\beta}{dt}(T_{eq})
\]  

(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 \( \beta \) 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 \( T_{eq} \sim 4^\circ \text{C} \), and therefore only the nonlinear contribution should remain, as has been experimentally observed from protons absorption experiments in water [25].

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 \( 4^\circ \text{C} \) 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 a 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 \( \beta \) 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 amplitudes 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
theoretically in [28], and later further confirmed experimentally in [27] and in agreement with our simulations [23], the photoacoustic generation takes place mostly in the surrounding liquid rather than within gold nanoparticles, and it is therefore the temperature-dependence of the Gruneisen coefficient of water which drives the thermal nonlinearity, as described in the simple point-absorber model by Calasso et al. [15].

Fig. 2 summarizes additional quantitative results from [23,24], which justify the experimental approach presented in this work. This figure shows results obtained for a 40-nm diameter gold nanoparticle immersed in water and illuminated with a 4 ns (FWHM) laser pulse. First, Fig. 2(a) predicts that a relative low fluence (typically a few mJ/cm²) is sufficient to obtain a significant nonlinear dependence of the photoacoustic peak-to-peak amplitude with the incident fluence. Second, Fig. 2(b) shows that the nonlinearity is predicted mostly around the center frequency corresponding to that of the temporal derivative of the laser pulse, i.e. approximately 100 MHz here. This feature has apparently never been mentioned nor received any attention to the best of our knowledge. It is however very important for experimental implementation as it suggests that a high frequency ultrasound detection should be used to measure thermal nonlinear effects in photoacoustics. Third, when one considers the evolution of the photoacoustic amplitude as a function of the equilibrium temperature, two different situations may be predicted, as shown in Fig. 2(c); in the linear regime (small temperature rises, \( \beta(T) \sim \beta(T_{eq}) \)), the temperature dependence of the photoacoustic amplitude simply reflects the temperature dependence of the coefficient of thermal expansion, as is well known [29,30]. However, when large transient temperature rises are involved (50 °C for instance in Fig. 2(c)), i.e. when nonlinear contributions are significant, the temperature-dependence of the photoacoustic amplitude now reflects some effective value of the coefficient of thermal expansion. In particular, a significant photoacoustic amplitude is predicted around \( T_{eq} \sim 4 \) °C.

3. Material and methods

A photoacoustic microscope was used to detect signals from a tube filled with absorbing aqueous solutions. The experimental setup is illustrated in Fig. 3. Nanosecond pulses from a Q-switched laser (Brilliant, Quantel, France) – wavelength of 532 nm, 4 ns pulse duration, 10 Hz repetition rate – were directed towards the sample. The beam was shaped by the combination of a lens (\( f = 75 \) mm, LA1608, Thorlabs, USA) and an engineered diffuser (EDC-10, RPC Photonics, USA) so that the laser illumination was homogeneous on the tube in the focal region of the transducer. The photoacoustic signals were detected with a 20 MHz spherically focused transducer (12.7 mm focal distance, 6.3 mm diameter, PI20-2-R0.50, Olympus, Japan), amplified (DPR500, remote pulser RP-L2, JSR Ultrasomics, USA) and digitized with an oscilloscope (DLM 2024, Yokogawa, Japan). A high frequency transducer was chosen to favor the observation of photoacoustic nonlinearities, as suggested by the theoretical predictions (Section 2.2).

Polycarbonate tubes with a 100 μm inner diameter (200 μm outer diameter, CTPC100-200, Paradigm Optics, USA) were used to approximately match the frequency of the emitted photoacoustic waves to that of the transducer. The tubes were filled with aqueous solutions of either 40-nm diameter gold nanospheres (HD.GC40.D10, BBI Solutions, UK) or an organic blue dye (colorant E133, acidifier E330, preservative E202, ScrapCooking, France). The dilutions for each type of absorber were set to obtain similar optical densities of about 10 (±0.1) at 532 nm. This excitation wavelength was chosen as it is close to the absorption peak of gold nanospheres with diameters on the order of a few tens of nanometers.

For both samples, the peak-to-peak amplitude of the photoacoustic signal was studied as a function of either the incident fluence or the equilibrium temperature. The tubes were immersed in a large water tank providing a slowly varying equilibrium temperature \( T_{eq} \) when the water temperature was different from the room temperature. The temperature was monitored using a thermocouple (type K, RS Components, UK) placed in the vicinity of the tube, and connected to a computer via a thermocouple data logger (TC-08, Pico Technology, UK). A magnetic stirrer was used to maintain a homogeneous temperature distribution in the water tank. The tube was fixed on a beaker to prevent motion induced by water convection. A hot air flow was used to prevent condensation to form and perturb the laser beam on the entrance wall of the water tank. The incident fluence was controlled using a laser-integrated variable attenuator. For each position of the attenuator, the fluence values on the sample were deduced from a prior calibration and direct measurements of the average laser output powers using a thermal power meter. From one sample to the other, only the position of the tube was adjusted so as to be in the focus of the transducer and within the area where the calibration for the fluence remained valid. To improve the signal-to-noise ratio, the signals were coherently averaged on the oscilloscope (\( N_{av} = 32 \)), before the peak-to-peak value computed on the oscilloscope was transferred to the computer. The system noise was estimated from measurements with no illumination on the samples.

For two equilibrium temperatures \( T_{eq} = 4 \) °C and \( T_{eq} = 20 \) °C, the fluence was varied from 0 mJ/cm² up to approximately 7 mJ/cm². For \( T_{eq} = 4 \) °C, water cooled in a freezer was used, the temperature of the tank remained around 4 ± 0.5 °C during the few minutes of

Fig. 2. Theoretical predictions from numerical simulations [23] of the photoacoustic emission by a single gold nanoparticle (40 nm in diameter) immersed in water, illuminated by 5-ns laser pulses. (a) Peak-to-peak amplitude vs incident fluence at \( T_{eq} = 20 \) °C. (b) Normalized frequency spectra for three values of the incident fluence, obtained by Fourier transformation of the photoacoustic signals. Each spectra was first individually normalized by the incident fluence, before all spectra were normalized to common arbitrary units. The spectrum in continuous line corresponds to that obtained in the linear regime. (c) Evolution of the normalized peak-to-peak amplitude as a function of the equilibrium temperature, obtained in the linear (insignificant temperature rise) and nonlinear (significant rise of the absorber temperature) regimes.
4. Results and discussion

Fig. 4(a) shows typical results obtained for $T_{eq} = 20 \degree C$. No nonlinearity is observed for both types of absorbers as the peak-to-peak amplitude of the photoacoustic signal increased linearly with the fluence. However, when the temperature was approximately $T_{eq} = 4 \degree C$, no photoacoustic signal could be detected from the solution of dye molecules, whereas a photoacoustic signal well above the noise floor could be observed from the solution of gold nanospheres. Moreover, the photoacoustic amplitude from the gold nanospheres shows a clear nonlinear dependence with the incident fluence. At $T_{eq} = 20 \degree C$, the fact that a linear behavior was observed as a function of $T_{eq}$, as opposed to what is predicted from Fig. 2(a), is likely due to the fact that the detection bandwidth centered around 20 MHz is not high enough to observe a significant nonlinear contribution: Fig. 2(a) indeed predicts the peak-to-peak evolution as a function of $T_{eq}$ for a single nanosphere, whereas the experiments were performed with an irradiated ensemble of particles distributed inside a tube of inner diameter 100 $\mu$m. Experimental signals were therefore bandpass-filtered around 20 MHz by both the spatial distribution of absorption and the transducer frequency response, reducing the weight of the nonlinearity expected to be the most significant around 100 MHz (see Fig. 2(a)). On the other hand, the fact that a photoacoustic signal of significant amplitude is observed with gold nanospheres at $T_{eq} \approx 4 \degree C$, whereas under the same condition none is observed from the solution of dye molecules, can be explained by the dynamic change of $\rho(T)$ around the nanosphere caused by the significant temperature rise. In this case, although the nonlinear generation is predominantly centered at much higher frequency than the detection frequency, it is the vanishing linear contribution at $T_{eq} \approx 4 \degree C$ that makes the nonlinear contribution detectable. For $T_{eq} = 20 \degree C$, the nonlinear contribution is probably too small compared to the linear one. With much larger nanospheres (200 nm in diameter) and much higher fluences (on the order of 70 mJ/cm$^2$), Egerev and Oraevsky [28] did observe a nonlinear contribution, on the order of twice the linear contribution.

When the photoacoustic signal was measured as a function of the equilibrium temperature, as illustrated in Fig. 5, for a fluence of 5 mJ/cm$^2$ (at which a nonlinear contribution was seen at $T_{eq} \approx 4 \degree C$ from the gold nanospheres), the experimental results agreed with the predictions from Fig. 2(c): the temperature dependence of the photoacoustic signal is significantly affected by the nanoscale local heating of the water surrounding the nanoparticles.

Several conclusions can be drawn from these experimental results. First, two absorbing media with the same optical density...
can be discriminated either from the dependence of the photoacoustic amplitude with the incident fluence or from its dependence on the equilibrium temperature, if significant changes of the coefficient of thermal expansion take places during the laser illumination for one of them. For gold nanoparticles, such changes reflect temperature rises at the nanoscale. Thermal-based photoacoustic nonlinearity could be easily observed with gold nanoparticles in water, with a detection frequency bandwidth centered around 20 MHz, at relatively low fluence provided that the temperature is close enough to 4 °C so that the linear contribution is negligible. To date, only one experimental study has reported the observation of presumably thermal-based photoacoustic nonlinearity in tissue [22]. However, the required temperature rise was suggested to arise from the aggregation of nanoparticles within cells which led to some heat confinement, rather than from temperature rise around individual nanoparticles as considered in our work (it was verified through the absorption spectrum of the solution that no aggregation occurred with our samples). It may be hypothesized that one reason for the lack of studies reporting thermal-based photoacoustic nonlinearity in tissue with nanoparticles may be that most experiments have used rather low frequency detection (in the MHz range), in combination with the limitation on fluence required by safety considerations (typically 20 mJ/cm²). Further work needs to be done to assess whether it can be possible to detect the nonlinear contribution in tissue at physiological temperature (Trev ≈ 37 °C) by using a higher frequency ultrasound. Photoacoustic systems operating at frequencies up to 125 MHz have recently been reported [31,32]. For in vitro applications, for which it may be envisaged to image samples at a controlled temperature, our results suggest that if biological tissue behaves as water, high frequency photoacoustic microscopy realized at a temperature close to 4 °C may allow discriminating nanoparticles from endogenous absorption, a feature that may be interesting for experimental studies of particle uptake in tissue for instance. Our study also suggests that the temperature dependence of the photoacoustic amplitude, a feature that has been proposed as a mean to monitor temperature changes in tissue during thermal therapies [29,30], may not only depend on the type of tissue, but if thermal nonlinearities are involved, may also depend on both the incident fluence and the type of absorbers used to photoacoustically probe the medium.

5. Conclusions

As a main message from our results, nanoscale temperature rises were observed either as a nonlinear dependence of the photoacoustic amplitude as a function of the incident fluence, or as a fluence- and absorber-dependent relationship between the photoacoustic amplitude and the equilibrium temperature, and permitted discrimination between two solutions (dye molecules and gold nanoparticles) of identical optical density. The relevance of these results to biomedical applications requires further work but imaging with controlled temperature (in particular close to 4 °C to enhance signals from localized temperature rise around nanosized contrast agents) could be envisioned with ex vivo tissue biopsies for instance.

Conflict of interest

The authors declare that there are no conflicts of interest.

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Olivier Simandoux received a Master degree in Science and Engineering from Institut d’Optique, Paris, France and ESPCI ParisTech, Paris, France, as well as a Master degree in Physical Acoustics from Université Paris Diderot, Paris, France, in 2011. He is currently working towards a Ph.D. degree at Institut Langevin at ESPCI ParisTech-CNRS where he is working on photoacoustic microscopy and cancerous tumors imaging.

Amaury Prost received his Master degree in Science and Engineering from ESPCI ParisTech, Paris, France, in 2010. He recently received his Ph.D. degree in Physics in April 2014 for his work on photoacoustics applied to ultrasound therapy and modeling the photoacoustic generation by nanoparticles.

Jérôme Gateau received his Ph.D. degree in physics (ultrasonics) in 2011 from University Paris VII, Paris, France, for his work on ultrafast ultrasound imaging of cavitation events in biological tissues and its application to ultrasonic therapy and detection mapping. He worked as a postdoctoral researcher with the Institute for Biological and Medical Imaging (IBMI), Munich, Germany from 2011 to 2013, where he focused his research interests on 3D optoacoustic imaging of small animals at mesoscopic and macroscopic scale, and intra-operative applications. He is currently working as a postdoctoral researcher with the Institut Langevin on mesoscopic photoacoustic imaging with contrast agents and optical wavefront shaping with photoacoustic feedback.

Emmanuel Bossy received his Ph.D. degree in 2003 from the Université Pierre et Marie Curie, Paris, France, for his contributions to quantitative ultrasonic characterization of bone. From 2003 to 2004, he was a postdoctoral research assistant at Boston University. At that time, his research oriented towards biomedical imaging techniques involving the combination of light and ultrasound in soft tissue. In 2004, he joined the Laboratoire d’Optique Physique at ESPCI ParisTech-CNRS, now Institut Langevin, where he has been working as an Associate Professor on photoacoustic and acousto-optic imaging, and non-destructive testing with ultrasound.