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Modeling photoacoustic spectral features of micron-sized particles

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Abstract
The photoacoustic signal generated from particles when irradiated by light is determined by attributes of the particle such as the size, speed of sound, morphology and the optical absorption coefficient. Unique features such as periodically varying minima and maxima are observed throughout the photoacoustic signal power spectrum, where the periodicity depends on these physical attributes. The frequency content of the photoacoustic signals can be used to obtain the physical attributes of unknown particles by comparison to analytical solutions of homogeneous symmetric geometric structures, such as spheres. However, analytical solutions do not exist for irregularly shaped particles, inhomogeneous particles or particles near structures. A finite element model (FEM) was used to simulate photoacoustic wave propagation from four different particle configurations: a homogeneous particle suspended in water, a homogeneous particle on a reflecting boundary, an inhomogeneous particle with an absorbing shell and non-absorbing core, and an irregularly shaped particle such as a red blood cell. Biocompatible perfluorocarbon droplets, 3–5 μm in diameter containing optically absorbing nanoparticles were used as the representative ideal particles, as they are spherical, homogeneous, optically translucent, and have known physical properties. The photoacoustic spectrum of micron-sized single droplets in suspension and on a reflecting boundary were measured over the frequency range of 100–500 MHz and compared directly to analytical models and the FEM. Good agreement between the analytical model, FEM and measured values were observed for a droplet in suspension, where the spectral minima agreed to within a 3.3 MHz standard deviation. For a droplet on a reflecting boundary, spectral features were correctly reproduced using the FEM but not the analytical model. The photoacoustic spectra from other common particle configurations such as...
particle with an absorbing shell and a biconcave-shaped red blood cell were also investigated, where unique features in the power spectrum could be used to identify them.

Keywords: photoacoustics, finite element method, spectral analysis

Online supplementary data available from stacks.iop.org/PMB/59/5795/mmedia

(Some figures may appear in colour only in the online journal)

1. Introduction

The photoacoustic effect is the emission of a pressure wave from a structure after irradiation by an energy source, typically a laser. For spatial scales of interest in biomedical photoacoustic imaging, a portion of the frequency of the emitted wave is in the ultrasonic range. This wave is called a photoacoustic or optoacoustic wave due to the laser-induced method in which it was generated (Wang 2009). Photoacoustic imaging requires an optical absorbing structure in the medium for a wave to be generated. Most tissues have negligible optical absorption throughout the visible and infrared spectrum where photoacoustic imaging is commonly used. The main absorbing structure in tissue is the blood, and the main chromophore in the red blood cells (RBCs) is haemoglobin. This endogenous source of contrast has been exploited in vivo for the detection of tumours (Zhang et al 2006), photoacoustic tomography (Wang and Hu 2012), functional imaging of the brain (Wang et al 2003, Nasiriavanaki et al 2013, Tsytsarev et al 2013), and imaging the vasculature (Kolkman et al 2003, Beard 2011). In addition, exogenous photoacoustic contrast agents with high contrast properties have been used to help identify breast, prostate and brain tumors (Manohar et al 2007, Agarwal et al 2007, Kim et al 2009, Yao et al 2013).

Recently, perfluorocarbon (PFC) emulsions loaded with absorbing nanoparticle (NPs) have gained popularity as theranostic agents (Strohm et al 2010, 2011, Wilson et al 2012). The optical absorbing nanoparticles are a necessary component for the generation of photoacoustic signals, as PFC liquids have negligible absorption in the visible and near-infrared wavelengths. When irradiated with sufficient optical energy, the NP-loaded micron-sized droplets emit photoacoustic signals. These contrast agents have unique signal signatures compared to endogenous photoacoustic sources in tissue, and these signatures can be used to localize and quantify the amount of agent present. Since this photoacoustic signal signature is more readily differentiated in the frequency domain, a model that can rapidly and accurately represent the frequency content of the signal is important for agent optimization and detection.

When a particle absorbs energy, it undergoes a rapid thermoelastic expansion that results in the emission of a photoacoustic wave in the ultrasonic frequency range. Neglecting viscosity and thermal conduction, the photoacoustic waves generated due to absorption of optical energy $H$ (such as a laser) is the solution to the inhomogeneous wave equation

$$\frac{1}{c^2} \frac{\partial^2 p}{\partial t^2} - \nabla^2 p = \frac{\beta}{C_p} \frac{\partial H}{\partial t}$$

where $p$ is the pressure, $t$ is time, $c$ is the sound speed, $\beta$ is the thermal expansion coefficient, and $C_p$ is the heat capacity (Morse and Ingard 1968). Analytical solutions for the generation of photoacoustic waves have been derived for simple geometries just as spheres (Diebold et al 1990). Assuming the pressure wave and energy source vary with time as $\exp(-\text{i}\omega t)$, the
solution to equation (1) for the photoacoustic waves generated from a liquid homogenous spherically symmetric particle is

\[ P(f) = i \frac{\mu_a I_0 \delta f}{4\pi C_p(r/a)} \left( \sin q - q \cos q \right) \left( \sin q + q \right) = \cos q + i \frac{\rho}{\rho^2} \sin q \]

where \( f \) is the frequency, \( a \) is the particle radius, \( \mu_a \) is the optical absorption coefficient, \( I_0 \) is the incident laser intensity, \( \rho \) is the density, the subscripts \( p \) and \( f \) refer to the particle and fluid, respectively, and \( q = \frac{2\pi f a}{\rho c_p} \) (Diebold and Westervelt 1988). Good agreement has been found between analytical solutions and measured photoacoustic signals for liquid homogeneous spheres (Diebold et al 1990). However, the analytical solution breaks down for complex configurations such as multi-particle systems, particles near boundaries, or particles that have a heterogeneous composition. In these cases, the photoacoustic signal must be numerically simulated. Several tools exist for calculating the photoacoustic signal; the k-wave toolbox calculates the time domain signal using coupled first order acoustic equations (Treeby and Cox 2010); Field II simulates the ultrasound field using linear systems theory (Jensen and Svendsen 1992, Jensen 1996); and COMSOL Multiphysics (Comsol, USA) uses a finite element model (FEM) to simulate the photoacoustic signal propagation in either the time or frequency domain.

In a FEM, the system is divided into smaller components which can then be iteratively solved. Recently, photoacoustic FEMs have examined temperature and displacement effects in tissue (Xu 2004, Xu et al 2006), photoacoustic tomography reconstruction (Yuan and Jiang 2007, Yao and Jiang 2009) and photoacoustic propagation in tissue (Wang et al 2012). A FEM was used to investigate the photoacoustic spectral content of photoacoustic waves generated in cases where the analytical solution cannot be used. The model takes into account wave generation and propagation immediately after the particles are irradiated and absorb the laser energy, and assumes that the particle instantly and uniformly absorbs the laser energy resulting in a pressure increase relative to the surrounding non-absorbing areas. The FEM then solves for the propagation of the acoustic waves due to the pressure differential within the system using the wave equation

\[ \frac{1}{c^2} \frac{\partial^2 p}{\partial t^2} - \nabla^2 p = 0. \]

The FEM solution was solved for four different geometries (figure 1): 1) a particle in suspension, 2) a particle on a highly reflecting boundary, 3) a non-homogeneous particle with an absorbing shell and non-absorbing core, and 4) an irregularly shaped particle. For a particle in suspension (scenario 1), the pressure waves simply radiate outwards and attenuate within the surrounding medium. For a particle near a boundary (scenario 2), waves emitted from the droplet will be reflected by the boundary back into the droplet. Scenario 3 simulates a particle with an inhomogeneous composition, a thin shell of optical absorbing material surrounding a non-absorbing liquid core. This simulates contrast agents where the optical absorbing material is contained in the shell instead of the core (Lovell et al 2011, Huynh et al 2012, Sun et al 2013). Scenario 4 simulates an irregularly shaped particle, for example a RBC with a bi-concave shape. Scenarios 1 and 2 were compared to experimental photoacoustic measurements of micron-sized PFC particle containing NPs as optical absorbers, while scenarios 3 and 4 demonstrate how the FEM could be used where analytical solutions do not exist.

This study shows that the photoacoustic power spectrum can be used to extract information about the particle that cannot be obtained using time domain methods alone. Using the FEM, matching solutions to the analytical equation were found for ideal cases such as a particle in
suspension. In the case where the analytical model cannot be used, the FEM correctly predicts the extra spectral features as measured from particles on a boundary. The FEM can be applied for even more complex systems, providing insight into how the frequency content of the photoacoustic waves is modified as a function of the particle/boundary characteristics.

2. Method

2.1. Perfluorocarbon droplets

Lead sulphide (PbS) nanoparticles were synthesized, coated with silica (Yi et al 2005, Gorelikov and Matsuura 2008), then fluorinated for miscibilization into PFP (Synquest, USA) (Matsuura et al 2009, Gorelikov et al 2011). PbS-loaded PFP droplets were prepared using 5 mL deionized water, 0.15 mL PFP solution containing PbS nanoparticles, and 0.03 mL anionic fluorosurfactant (Zonyl FSP, Sigma-Aldrich, USA) using emulsification with 10 μm pore polymer membranes (Whatman, USA), following coarse emulsification by vortexing. The droplet diameters were measured using a microscope with an optical scale.

2.2. Photoacoustic measurements

A SASAM photoacoustic microscope (Kibero GmbH, Germany) was used for all measurements and is described in detail in reference (Strohm et al 2011). Briefly, a 1064 nm laser was focused by a 10 × objective (0.30 numerical aperture) onto the sample from below, and a 375 MHz transducer (60° aperture, 42% bandwidth) positioned above the sample recorded the photoacoustic signals generated by the sample. The laser was operated at a 2 kHz pulse repetition frequency with a 700 ps pulse width. This pulse width was less than the stress and thermal confinement times of a 1 μm diameter liquid PFC droplet, calculated to be 2 ns and 8 μs, respectively. The signals were amplified by 40 dB (Miteq, USA) and digitized at 8 GS s⁻¹ (0.125 samples ns⁻¹). All measurements were made at 36 °C. The droplet diameter was found by comparing the recorded image to a calibrated scale using the 10 × objective. The error associated with this optical measurement is ±0.5 μm when using a 10 × objective, primarily due to the small particle sizes examined.

The photoacoustic signals from particles in suspension and on a boundary were investigated using micron-sized nanoparticle-loaded droplets (figure 2). In scenario #1, a droplet deposited on top of an agar gel surrounded by water was used to approximate a droplet in suspension. The agar gel has similar properties as water (Zell et al 2007) and minimized any

![Figure 1.](image-url)
reflections that might occur. In scenario #2, the droplet was deposited directly on the glass substrate, a highly reflecting surface for ultrasound. All measurements averaged 100 RF-lines to increase the signal to noise ratio (SNR). The transducer response was removed from the signal by normalizing the signal as described in (Baddour et al. 2005), then a Hamming window and 100–500 MHz bandpass filter were applied. These processed signals were then compared to the analytical model and FEM solution.

2.3. The finite element model

Finite element models for each scenario were solved using the COMSOL Multiphysics (COMSOL, USA) software package. A transient acoustics 2D axisymmetric model was used to calculate the photoacoustic emission from particles using the wave equation (equation (1)). For this calculation, the particle diameter must be known, but the error associated with optical imaging for particles <5 μm in diameter is ±0.5 μm. Since the exact diameter could not be accurately measured, simulations were completed with a range of diameters similar to the measured diameter. The simulation with the most similar photoacoustic spectrum compared to the experimental results was used. In the model, the initial pressure was set to unity inside the particle, and zero elsewhere. For scenario 3, a particle with an absorbing polymer shell was simulated where the pressure within the shell of thickness 250 nm was set to unity, and zero elsewhere including the droplet core. The shell was composed of Poly-lactide-coglycolic acid (PLGA), which has a known density (1340 kg m⁻³) and sound speed (2300 m s⁻¹) (Parker et al. 2010). The model assumed the laser energy was absorbed instantaneously (infinitesimally narrow laser pulse) so that the pressure wave did not propagate prior to the start of the simulation. The mesh within the particle was set to 0.01 μm, and 0.05 μm outside. An absorbing boundary condition was set at a 10 μm radius, the outer boundary of the simulation. The photoacoustic signal directly above the particle
was recorded as a function of time with a 0.125 ns step size (the same as the experimental acquisition rate). Diagrams of the four modeling scenarios are depicted in figure 3. The FEM simulated a propagation time of 80 ns, which took approximately 3–5 h for 800000 degrees of freedom using a computational cluster containing six dual-core Opteron nodes and 40 GB of memory. The parameters used in the model are listed in table 1, including the diameter measured optically and the final diameter determined by a comparison between measured and simulated photoacoustic signals. Measurements from four droplet sizes were used in this study to compare to the theoretical models: one droplet in suspension, and three droplets on a glass substrate.
The speed of sound is a required parameter in the simulations. The boiling point of bulk PFP is 29 °C, and experiments were performed at 36 °C. The PFP liquid inside the droplets exists in a superheated state where the boiling point is increased by 40–50 °C compared to the bulk phase (Kripfgans et al. 2000); therefore it is difficult to measure the properties of bulk liquid PFP at temperatures greater than 29 °C. Studies measured the sound speed of PFP to be 468 m s\(^{-1}\) using 2 MHz at 22 °C (Jongsma 1979) and 477 m s\(^{-1}\) using 1 MHz at 25 °C (Narayana and Swamy 1989). Measurements of several PFC liquids other than PFP showed a linear decrease in sound speed with increasing temperature from 25–36 °C at 10 MHz (Marsh et al. 2002). The change in sound speed was \(\pm 0.778\) m s\(^{-1}\) °C\(^{-1}\) for FC-72, the liquid with the closest molecular weight and structure to PFP. Assuming the change in sound speed with temperature of PFP is similar to the FC-72 even when in a superheated state, the sound speeds of 468 m s\(^{-1}\) (22 °C) and 477 m s\(^{-1}\) (25 °C) would be 429 m s\(^{-1}\) and 446 m s\(^{-1}\) at 36 °C, respectively. Averaging these values gives 438 m s\(^{-1}\), which was used in the FEM and analytical simulations. Sound dispersion was neglected as it was found that PFC liquids have only a 1.5% increase from 100–1000 MHz (Strohm and Kolios 2011) and considered negligible over the frequency range used in this study.

The properties of the red blood cell were different than the droplets. The size and shape were calculated using an equation derived empirically (Evans and Fung 1972). The RBC geometry is shown in figure 3(d). The sound speed used in the model was 1650 m s\(^{-1}\) (similar to other sound speeds measured (Dukhin et al. 2006, Mohamed et al. 2012)) and the density was 1100 kg m\(^{-3}\) (Godin et al. 2007, Grover et al. 2011). The blood cell interior was assumed to be homogeneous throughout, both optically and acoustically.

3. Results

3.1. Finite element model validation

The FEM solutions of two PFP droplets (3.1 μm and 5.0 μm) suspended in water were calculated using COMSOL with the parameters described in table 1. The photoacoustic signal was calculated as a function of time at a point on the outer system boundary over an 80 ns time length. The FEM solution was compared to the analytical solution (equation (2)) using identical parameters. The signals were normalized to maximum amplitude, and no other signal processing methods or filters were applied. Good agreement in both the time and frequency domains were observed as shown in figure 4, thus validating the FEM methodology.

3.2. Particles in suspension and on a glass boundary

The simulated time domain and power spectrum for a 3.1 μm droplet in suspension and on a glass substrate using the analytical solution (equation (2)) and the results are shown in figure 5. The parameters used for modeling the droplet in each case were identical. Both scenarios show spectral minima around 200, 345, 490 and 635 MHz, however, the spectrum from the droplet on glass has additional spectral minima located around 275, 405 and 540 MHz.

The measured time domain signal for a 3.1 μm droplet on agar (simulating a droplet in suspension) and a 3.1 μm droplet on the glass substrate are shown in figures 6(a) and (b), respectively. These signals appear different than the simulations in figure 5 as they are band-limited due to the limited transducer response. Despite similar droplet sizes, the signal from the droplet on a glass boundary exhibits additional signal information. This is a result of the pressure wave rebounding from the glass substrate back towards the transducer, which can alter the frequency content of the photoacoustic signal.
Figure 4. Theoretical waveform and spectrum 3.1 μm droplet (top) and a 5.0 μm droplet (bottom) suspended in water obtained from the analytical solution (equation (2), solid black line) and the FEM solution (dotted red line). The signals were normalized to the maximum signal amplitude for comparison. The good agreement in both the time and frequency domains validate FEM methodology.
The corresponding power spectra of the two 3.1 μm droplets, along with three other droplets of different diameters measured on a glass substrate, are shown in figure 7. In figure 7(a) (droplet in suspension) the frequencies of the spectral minima at 203, 347 and 492 MHz of the FEM and analytical solution are in good agreement with the measured signal from the droplet (spectral minima located at 205, 348 and 481 MHz). For droplets on glass, the FEM correctly predicts the additional spectral minima that are absent in the analytical solution. Table 2 lists the frequencies of the spectral minima from the measured signal as well as from the analytical and FEM solutions. In all cases, the average standard deviation between the FEM and measured values were less than 8 MHz.

3.3. Irregular particles

The FEM can be applied towards other particle configurations, such as a particle with heterogeneous absorption (particle with an absorbing shell, scenario 3) and an irregularly shaped particle (a red blood cell, scenario 4).
The FEM was applied to a particle with an optical absorbing shell surrounding a non-absorbing liquid core as shown in figure 3(c). No analytical solution exists for this configuration. Contrast agents with this configuration are under development for use as ultrasound and photoacoustic contrast agents and for cancer therapy, such as polymer-based particles (Kohl et al. 2011, Sun et al. 2013, Wang et al. 2014), liposomes (Volodkin et al. 2009), porphysomes (Lovell et al. 2011) and microbubbles (Huynh et al. 2012). In the FEM, the pressure in the

Table 2. Spectral minima frequencies of the four droplets in figure 7. The spectral minima associated with the glass substrate are not observed using the analytical model are italicized. The last column is the average standard deviation between the frequency minima of the FEM and measured spectrum.

<table>
<thead>
<tr>
<th>Droplet</th>
<th>Analytical model (MHz)</th>
<th>FEM (MHz)</th>
<th>Measured (MHz)</th>
<th>Standard deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>203, 347, 492</td>
<td>203, 347, 492</td>
<td>205, 348, 481</td>
<td>3.3 MHz</td>
</tr>
<tr>
<td>2</td>
<td>218, 385, 544</td>
<td>219, 295, 377, 457, 533</td>
<td>217, 295, 379, 457, 527</td>
<td>1.4 MHz</td>
</tr>
<tr>
<td>3</td>
<td>202, 347, 491</td>
<td>201, 277, 346, 406, 490</td>
<td>215, 279, 346, 422, 484</td>
<td>6.1 MHz</td>
</tr>
<tr>
<td>4</td>
<td>173, 299, 422</td>
<td>170, 230, 297, 347, 416</td>
<td>197, 228, 309, 350, 426</td>
<td>7.6 MHz</td>
</tr>
</tbody>
</table>
shell was set to unity, with the core and surrounding fluid pressure set to zero. All other parameters were the same as scenario 1 (see table 1). The location of the spectra minima and maxima shifted compared to the analytical solution that assumes a homogeneous uniformly absorbing sphere (figure 8). The distance between the spectral minima increased slightly with increasing frequency (from 152 MHz between minima at 200 MHz–164 MHz between minima at 600 MHz), while the distance between the minima was constant for the analytical solution of the uniformly absorbing sphere. The shift in the location of the spectral peaks may be sufficient to differentiate an absorbing particle versus an absorbing shell, however, it is unlikely the shell thickness could be estimated using this procedure.

Red blood cells are shaped like a bi-concave disk with an average diameter of 7.8 μm and a height of 1–2 μm (Wintrobe et al 2009). These irregularly shaped particles cannot be modeled using analytical methods, and are typically approximated as spheres or ellipsoids (Ahuja and Hendee 1977, Saha and Kolios 2011). The FEM is well suited for modeling the photoacoustic signals generated from red blood cells. All parameters were the same as scenario 1 except the shape, density and sound speed (see table 1). The signals were calculated as a function of angle, with a horizontally aligned blood cell (angle of 0°, with the transducer above the cell as depicted in figure 3(d)), and a vertically aligned blood cell (angle of 90°, with the transducer to the right of the cell as depicted in figure 3(d)).

The spectral features shift as a function of measured angle as shown in figure 9. At 0°, minima occur at approximately 200, 450, 750 and 950 MHz. As the blood cell rotates, the spectral minima and maxima shift to higher frequencies. A horizontally oriented blood cell has only one minimum at 800 MHz (Strohm et al 2013a, 2013b). The spectra nearly overlap in the 0–100 MHz frequency range. This indicates that the signal is similar regardless of the blood cell orientation, and suggests that the cells can accurately be modeled as a sphere or ellipsoid for computational efficiency within this limited frequency range. However when using frequencies greater than 100 MHz, the blood cell should be modeled as a bi-concave shape as the spectrum depends on the orientation (Strohm et al 2013b).

3.4. Visualization of the propagating signal

Animations generated from the FEM simulation show the pressure wave expansion from particles in the four scenarios: a 3.1 μm droplet in suspension, a 3.1 μm droplet on a glass
substrate, a 3.1 \( \mu \)m particle in suspension with a shell, and a 7.8 \( \mu \)m single red blood cell (see supplementary data stacks.iop.org/PMB/59/5795/mmedia). These videos enable visualization of the acoustic wave propagation from the different particles. In all scenarios, a positive pressure wave (red) is shown propagating away from the particle surface, with a negative pressure wave (blue) traveling toward the center. The negative pressure wave then travels outward away from the droplet. This is responsible for the characteristic ‘N’ shape typically observed in photoacoustic measurements of spherical objects, which is analogous to the pressure distribution observed during a bursting balloon (Deihl 1968). For the droplet on the glass substrate, the acoustic wave travels faster through the glass than the coupling fluid, due to the difference in sound speed (5600 m s\(^{-1}\) in glass compared to 1520 m s\(^{-1}\) in water). In the case of the absorbing shell (scenario 3), a narrow positive pressure acoustic wave is observed travelling away from the droplet, with a narrow negative pressure wave following a short time after. The wave propagation within the red blood cell is asymmetric due to its irregular shape, and the wave within the cell travels faster than in the other particles as the sound speed in the cell is three times larger than the sound speed in the droplet.

4. Discussion

The nanoparticle-loaded PFC droplets are ideal for photoacoustic measurements. The droplet can be considered homogeneous despite the presence of nanoparticles throughout. The number of nanoparticles in each droplet is calculated to be in the thousands, however the nanoparticles are small and occupy a negligible volume in comparison to the overall droplet volume (Strohm et al 2012). The nanoparticles are well dispersed within the volume, and thus upon irradiation, all nanoparticles absorb the energy uniformly and instantaneously. The end result is a photoacoustic wave with characteristics that depend on the droplet composition, not the nanoparticles. We have shown in previous work good agreement between experiment and theory for a nanoparticle loaded droplet in suspension (Strohm et al 2012).

Small changes in the photoacoustic time domain signal may not be sufficient to extract information about the particle. We have shown that micron-sized particles have unique spectral features over the wide ultrasound bandwidth used (100–500 MHz). These spectral features can be used to extract the particle parameters, such as their size and sound speed which can then be used for particle identification (Strohm et al 2012) or diagnosis of blood-related disease (Strohm et al 2013b). This is difficult using the time domain signal alone.
Analytical solutions describing the time and frequency domain photoacoustic signals exist for spherical homogeneous particles, but not for irregularly particles, particles near boundaries or inhomogeneous particles. This study shows that spectral features calculated using the FEM simulation are in good agreement with the analytical model for simple geometries such as a homogenous droplet in suspension, and gives accurate solutions where the analytical model breaks down, such as a droplet positioned on a reflecting boundary. For droplets on glass, the substrate reflects the pressure waves back through the droplet which are then recorded by the transducer. These additional waves result in additional spectral minima not observed from droplets in suspension. Figure 6 shows that the time domain signals for a droplet in suspension and on a reflecting boundary are visually different, but it is not possible to determine the particle parameters or boundary conditions using these signals alone. The corresponding power spectrum in figure 7 shows unique features that help identify these unknowns. Table 2 summarizes the frequency of the spectral minima for all droplets, where the average standard deviation of the frequency of the spectral minima between the FEM and measured was less than 8 MHz.

Our primary interest was the frequency content of the photoacoustic waves, however analytical solutions exist only for simple homogeneous geometries. The FEM could be applied to various scenarios where the analytical solution cannot be used, such as the generation of photoacoustic waves from multiple sources, heterogeneous absorbance and from asymmetric shapes such as the bi-concave shape of red blood cells where the photoacoustic spectral features are known to depend on RBC morphology (Strohm et al 2013b).

The amplitude parameters in equation (2) can be adjusted to optimize the photoacoustic signal generation from the droplets to a limited extent. Increasing the laser intensity \( I_0 \) is not necessarily feasible as there are limits on the intensities that can be used. The sound speed, thermal expansion coefficient and heat capacity are inherent to the PFC liquid used with small variation between PFC liquids. The easiest way to increase the photoacoustic signal is to increase the absorption coefficient inside the droplet (by increasing the number of nanoparticles or their absorption coefficient), or to increase the droplet size. This would increase the total absorption coefficient of the droplet, ultimately increasing the signal amplitude. Moreover, for theranostics, larger droplets will offer opportunities to carry a larger therapeutic payload for activated release by light directly at a tumor site. These high frequencies cannot be used \textit{in vivo} due to high attenuation of ultrasound, but could be used to identify cells and/or particles in samples using the photoacoustic spectrum. Understanding how the photoacoustic signal is generated by these particles and propagates in a medium assists in development and optimization of these particles for eventual use \textit{in vivo} using clinical ultrasound and photoacoustic instruments.

5. Conclusion

The photoacoustic power spectrum can be used to extract information about a particle that cannot be obtained from the time domain signal alone. Analytical solutions can be used to calculate the photoacoustic signal from simple geometries such as spheres, but cannot be used for irregularly-shaped particles or particles near boundaries. In those cases, a finite element method can be used to calculate the particle-dependent spectral features. The FEM can easily be adapted to other configurations such as multi-particle systems, and particles with heterogeneous absorption properties and/or boundary conditions where analytical solutions cannot be used. This study establishes that particle types can be identified according to unique spectral features in the photoacoustic spectrum.
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