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Monte-Carlo-based inversion scheme for 3D quantitative photoacoustic tomography

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ABSTRACT

The goal of quantitative photoacoustic tomography (qPAT) is to recover maps of the chromophore distributions from multiwavelength images of the initial pressure. Model-based inversions that incorporate the physical processes underlying the photoacoustic (PA) signal generation represent a promising approach. Monte-Carlo models of the light transport are computationally expensive, but provide accurate fluence distributions predictions, especially in the ballistic and quasi-ballistic regimes. Here, we focus on the inverse problem of 3D qPAT of blood oxygenation and investigate the application of the Monte-Carlo method in a model-based inversion scheme. A forward model of the light transport based on the MCX simulator and acoustic propagation modeled by the k-Wave toolbox was used to generate a PA image data set acquired in a tissue phantom over a planar detection geometry. The combination of the optical and acoustic models is shown to account for limited-view artifacts. In addition, the errors in the fluence due to, for example, partial volume artifacts and absorbers immediately adjacent to the region of interest are investigated. To accomplish large-scale inversions in 3D, the number of degrees of freedom is reduced by applying image segmentation to the initial pressure distribution to extract a limited number of regions with homogeneous optical parameters. The absorber concentration in the tissue phantom was estimated using a coordinate descent parameter search based on the comparison between measured and modeled PA spectra. The estimated relative concentrations using this approach lie within 5 %compared to the known concentrations. Finally, we discuss the feasibility of this approach to recover the blood oxygenation from experimental data.

Keywords: quantitative photoacoustic tomography, model-based inversion, oxygen saturation, chromophore concentration, photoacoustic imaging, Monte Carlo methods for light transport, boundary conditions, coordinate search

1. INTRODUCTION

Photoacoustic tomography (PAT) is a hybrid imaging method combining optical excitation of tissues and acoustic detection of the induced ultrasound waves.¹ The main advantages of PAT are based on its high contrast due to the spectral specificity of tissues, the low-scattering nature of ultrasonic waves, the large penetration depth of light in the near infrared regime causing a high depth-to-resolution ratio, and its ability to noninvasively provide in-vivo images at multiple spatial scales.²

In quantitative photoacoustic tomography (qPAT), the goal is to accurately determine the absolute concentration of light absorbing chromophores. One of the main contrast agents in PAT is blood in form of oxygenated hemoglobin and deoxygenated hemoglobin. The ratio of oxygenated hemoglobin and total hemoglobin sO_2 provides physiological information about the metabolism and changes in the vasculature, which makes it an important marker for a variety of pathologies characterized by metabolic or structural changes in the vasculature,³ e.g. tracking of tumor growth and therapy *in-vivo*.⁴ Model-based inversion schemes have been shown to be a promising approach for the recovery of chromophore concentrations from PA images quantitatively.^{5, 6}

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In order to determine sO_2 from PA images, multiwavelength measurements and some form of spectral unmixing, i.e. the recovery of the relative contribution of various chromophores to the PA signal, are required.⁷ Spectral unmixing at desirably high spatial resolution represents a large scale inverse problem that is ill-posed⁸ and non-linear because of the light fluence, which is a non-linear function of absorption in scattering media.

For the recovery of chromophore concentration from PA images, an accurate estimate of the light fluence within the imaged volume is required.⁷ Modeling the fluence accurately requires a light model that is valid not only in the diffuse regime, but also in the quasi-ballistic and ballistic regime, i.e. in proximity of the light source. Most previous studies employed fluence estimations based on the radiative transfer equation (RTE) or approximations thereof.^{9,10} Yet, analytical solutions of the RTE do not exist for arbitrary geometries, and numerical solutions are computationally expensive. Approximations of the RTE, however, assume diffuse light propagation, which is only valid for depths greater than a few scattering lengths inside the tissue (typically $\sim 10 \text{ mm}$), i.e. not near light sources which is a region of strong interest in PAT. Therefore, we use a Monte-Carlo based approach to model the light transport which approximates the RTE with any desired accuracy¹¹ and hence is accurate in all three regimes of interest.^{12, 13}

Another major challenge in recovering the chromophore concentration from PA images quantitatively is the difference between the true initial pressure distribution and the measured PA image due to e.g. limited detection aperture and the frequency response of the detectors.^{14,15} We aim to account for this by incorporating the limited detection aperture in the acoustic forward model¹⁶ and by using a Fabry-Pérot interferometer as the acoustic detector with high bandwidth and measured frequency response.

In this paper, we present a model-based approach that first reduces the scale of the inverse problem to a small number of unknowns using image segmentation, and then estimates the relative chromophore concentration in a tissue phantom using an iterative search that reduces the difference between measured and modeled PA spectra. This paper is structured as follows: The experimental setting using a tissue phantom is introduced in section 2.1, the two stage PA forward model and the image segmentation is explained in section 2.2. The parameter estimation framework is outlined in 2.3, and the MC light model is evaluated with respect to boundary effects and background absorbers in section 2.4. The results in section 3 comprise a comparison between measured and modeled data and the results of the parameter search providing the relative absorber concentrations utilized in the tissue phantom.

2. METHODS

2.1 Experimental setup

The PA imaging setup for acquiring 3D image sets consists of a simple tissue phantom that has been excited using laser pulses and a Fabry-Pérot interferometer (FPI) for detection of ultrasound waves. The system is based on previous work¹⁷ and is described in detail elsewhere¹⁸ *.

The tissue phantom consisted of three parallel fluoropolymer tubes that were filled with mixtures of CuSO4 and NiSO4 and immersed in diluted milk. A 3D view of the phantom is shown in Fig. 1 A, and a detailed schematic of the phantom is shown in Fig. 1 B. The three tubes were filled with aqueous solutions of CuSO4 (0.4 M) and NiSO4 (1.52 M) at different relative concentrations. The leftmost tube was filled with 76.6 % NiSO4 and 23.4 % CuSO4, the center tube was filled with 51.7 % NiSO4 and 48.3 % CuSO4, and the rightmost with 27.3 % NiSO4 and 72.7 % CuSO4. The spectrum of different CuSO4 and NiSO4 solutions is shown in Fig. 1 C.

3D image data sets were reconstructed using the k-Wave toolbox¹⁶ for Matlab. The image dimensions of the reconstructed images were $20 \times 20 \times 8 \text{ mm}^3$ with a spatial resolution of $dx = dy = dz = 70 \mu \text{m}$ (i.e. isotropic voxelsize). The recorded PA signals had been calibrated with the excitation pulse energy to account for the wavelength dependency of the energy emitted by the laser system.

^{*}A paper on the experimental setup entitled "Experimental validation of a Monte-Carlo-based inversion scheme for 3-D quantitative photoacoustic tomography" is published in Proc. of SPIE 2017



Figure 1: A: 3D view of the phantom setting as result of the image segmentation based on the PA image. The reconstructed subvolumes for the three tubes is shown in blue, green and red. B: Schematic of the phantom as cross section. OD (ID) stands for the tubes' outer (inner) diameter, respectively. C: Absorption and scattering spectra of the phantom constituents. The left vertical axis indicates μ_a for the blue, black and red curves. The blue curve shows μ_a for a pure NiSO4 solution (1.52 M), the black curve shows pure CuSO4 (0.4 M) and the red a mixture with 50% of each. The right vertical axis corresponds to the dashed green curve indicating μ_s' of the surrounding scattering material.

2.2 Model description

The PA forward model consists of three components: a light transport model, an acoustic propagation model, and the reconstruction of the initial pressure distribution, which is later compared to the measured data. The first component models the light transport in the tissue phantom and provides an estimate of the absorbed energy distribution. The second component simulates the acoustic propagation of the sound waves induced by the absorbed energy inside the tissue phantom. The third step reconstructs the simulated PA times series in order to obtain $p_0^{sim}(\vec{r}, \lambda)$. An overview of the PA forward model is shown in Fig. 2. The tissue phantom used in the light model simulations had been reconstructed from the measured initial pressure distribution. The process is described in detail in section 2.2.2.



Figure 2: Schematic of photoacoustic forward model. Left: Output of a light transport simulation. Fluence distribution Φ seen for the center slice perpendicular to the tube axes. Color scale in arbitrary units represents high fluence in white and yellow and low fluence in black. From this the initial pressure distribution is computed and used as input for the acoustic forward simulation. Center: Pressure time series resulting from the acoustic propagation model for an initial pressure distribution as seen in the left figure. Vertical axis indicates time; horizontal axis indicates sensor position r_{sensor} ; color scale represents pressure intensity (high values in white and yellow, low values in red, negative values in black). Right: Reconstructed initial pressure distribution using time-reversal method including the limited aperture resulting from the planar FP sensor. The figure shows the same slice of the volume as in the left figure.

2.2.1 Light transport model

The light transport was simulated in 3D using the Monte Carlo eXtreme simulator (MCX),¹² which is parallelized for execution on GPUs. In the MC light model, virtual photons are launched at a given source position and

propagated as packets of energy through a volume defined by a regular grid of isotropic voxels. In this model, photons are launched according to a beam profile, which is of similar shape as a 2-dimensional Gaussian curve. Photons are scattered according to the scattering coefficient μ_s and the anisotropy parameter g of the current voxel (defined by its material type). Photons deposit energy in a voxel when leaving that voxel, thereby decreasing the weight of that photon packet according to the absorption coefficient of that voxel. The packet weight deposited in the current voxel is added to its probability distribution, from which the absorbed energy distribution H and fluence Φ is calculated according to:

$$H(\vec{r},\lambda) = \mu_a(\vec{r},\lambda)\Phi(\vec{r},\lambda).$$

The input to an MCX simulation was a volume file containing $400 \times 400 \times 130$ voxels identifying one material type for each voxel. For each material type, the absorption coefficient μ_a , the scattering coefficient μ_s , the anisotropy parameter g, and the refractive index n are given as input parameters. Each voxel has a size of $70^3 \ \mu\text{m}^3$, hence the total simulated volume is $28 \times 28 \times 9 \ \text{mm}^3$. In order to avoid limited volume effects on the resulting fluence (due to photons interacting with the volume boundaries), the light transport was simulated using a larger volume than the measured PA image, as studied in section 2.4. Four types of media were used in the simulations presented here, one homogeneous background (diluted milk), for which we assume that the absorption coefficient equals $\mu_a(\lambda)$ of water. The scattering coefficient of the background is represented by the green curve in Fig. 1 C. The remaining three material types correspond to the three tubes, for which a wavelength independent scattering coefficient of $\mu_s = 0.01 \ \text{mm}^{-1}$ and wavelength dependent $\mu_a(\lambda)$ as in Fig. 1 C has been assumed.

For the comparison between measured and modeled data described in section 3.1, the values for $\mu_a(\lambda)$ were computed according to the known ratio of NiSO4 and CuSO4 solutions in the tubes. Pure solutions had concentrations of $c_{\text{NiSO4}}^{\text{max}} = 1.52 \text{ mol/liter}$ and $c_{\text{CuSO4}}^{\text{max}} = 0.4 \text{ mol/liter}$, respectively. Hence, $\mu_a(\lambda)$ was computed for tube k using the known absorption spectra $\alpha_{NiSO4}(\lambda)$, $\alpha_{CuSO4}(\lambda)$, respectively, and the known mixture parameter R_k . Furthermore, we assumed that both substances contribute linearly to the total absorption coefficient:

$$\mu_{a,k}(\lambda, R_k) = R_k \cdot c_{\text{NiSO4}}^{\max} \alpha_{\text{NiSO4}}(\lambda) + (1 - R_k) \cdot c_{\text{cuSO4}}^{\max} \alpha_{\text{cuSO4}}(\lambda), \tag{1}$$

where $R_1 = 0.75$ for tube 1, $R_2 = 0.5$ for tube 2 and $R_3 = 0.25$.

For the parameter estimation procedure described in section 3.2, R_k and (thereby also μ_a) is considered unknown and varied during the parameter search. An overview of the optical parameters used for the different studies is given in Table 1.

material	$\mu_a \; [\mathrm{mm}^{-1}]$	$\mu_s \; [\mathrm{mm}^{-1}]$	n	g	Type of study
background (1)	$\mu_a^{H_20}(\lambda)$	$\mu_s(\lambda)$ see Fig. 1 C	1.33	0.9	Comparison measured
					vs modeled data
tubes (2)	$\mu_a(\lambda)$ see Fig. 1 C	0.1	1.33	0.9	Comparison measured
					vs modeled data
background (1)	2e - 2	10	1	0.9	Boundary conditions
tubes (2)	5	10	1	0.9	Boundary conditions

Table 1: List of optical parameters

For each MC light simulation we used $5 \cdot 10^7$ photons, which took approximately 1–2 minutes per simulation on a desktop GPU.¹⁹ As $\mu_a(\lambda)$ and $\mu_s(\lambda)$ are wavelength dependent, each measured wavelength requires a corresponding simulation of the light model for that particular parameter set. For the parameter search described in section 3.2 the number of photons was reduced to $5 \cdot 10^6$ to speed up the parameter estimation procedure.

The output of the light transport model is the absorbed energy distribution $H(\vec{r}, \lambda)$, from which the initial pressure distribution is computed using the Grüneisen parameter Γ :

$p_0(\vec{r},\lambda) = \Gamma H(\vec{r},\lambda).$

For simplicity we assumed a Grüneisen coefficient of 1 for all materials. The initial pressure distribution $p_0(\vec{r}, \lambda)$ gained from the result of a MC simulation serves as input to the acoustic propagation model, which will be described in section 2.2.3.

2.2.2 Image segmentation

The goal of the image segmentation is to reconstruct the geometry of the tubes from the measured pressure data. This way, the number of unknowns in the inversion scheme is reduced. That is, we do not seek the chromophore concentration at every voxel independently, but only for a small number of material types, whose continuous location were obtained through image segmentation. The optical parameters within one material type are assumed homogeneous.

The image segmentation applied here is not a framework that is generally applicable, e.g. to vessel networks. but rather represents a simple method using prior knowledge in order to proof the applicability of our modelbased inversion approach. The input to the image segmentation is the initial pressure distribution $p_0^{exp}(\vec{r})$ reconstructed from the measured pressure time-series for one excitation wavelength.

The image segmentation is based on the idea to search for local maxima in slices of p_0^{exp} perpendicular to the tube axes and to draw filled circles around the local maxima representing the tube centers. For this purpose, we make use of prior knowledge regarding the number, the shape, and the geometry of the tube absorbers.

First, a gaussian blur filter with $\sigma = 2$ voxels is applied to the raw data $p_0^{exp}(\vec{r})$ in order to reduce the impact of noise on the location of the local maxima. Then, the locations of three local maxima are extracted for each slice of p_0^{exp} perpendicular to the tube axes. The location of the maxima within one slice are assumed to represent the centers of the tubes. Around each local maximum, a filled circle with a radius of three voxels is drawn marking the voxels belonging to that tube. The reconstructed tubes resulting from our image segmentation approach are shown in Fig. 1 A with the original pressure data in gray. The result of the image segmentation is a volume identifying four different media types, which serves as input to the MC light transport simulations.

2.2.3 Acoustic propagation model

The input to the acoustic propagation model is the absorbed energy distribution $p_0^{MCX}(\vec{r})$ obtained from the results of the MC light transport simulations. The acoustic propagation model is simulated using the k-Wave toolbox¹⁶ for Matlab. Its purpose is to account for the limited aperture inherent to the planar detector geometry^{14,15} and its influence on the PA images. Homogeneous acoustic properties are assumed with a speed of sound of 1500 m/s and a density of 1000 kg/m³. The computational grid used by k-Wave was initialized with a spatial resolution of 70 μm and the standard temporal resolution defined by the sound speed. The initial pressure distribution $p_0^{sim}(\vec{r}, \lambda)$ is obtained using k-Wave's time-reversal method kspaceFirstOrder3DG and is accelerated by execution on a GPU. The result of the time-reversal based reconstruction $p_0^{sim}(\vec{r}, \lambda)$ is used for comparison with the measured pressure distribution $p_0^{exp}(\vec{r})$ shown in section 3.1.

2.3 Parameter estimation

The parameter estimation framework aims to determine the relative concentrations of NiSO4 and CuSO4 solutions in the tube phantom, represented by the parameters R_k , k = 1, 2, 3 in Eq. 1. Our approach is based on the comparison of PA spectra from measured and modeled data and the iterative update of the relative concentration in the model, depending on the residual difference between the PA spectra and the previously tested parameters. An overview of the approach is shown in Fig. 3. As the MC light model does not provide any analytical form for the fluence (and hence the pressure distribution), the possibility to compute gradients analytically is not given. Hence, we use an iterative, non-gradient optimization for the parameter estimation, which is described in the following. First, PA spectra are obtained from multi-wavelength simulations using the MC light model. Obtaining the PA spectra from the acoustic propagation model was omitted for the sake of execution speed, but yielded equal final concentrations (not shown).



Figure 3: This schematic gives an overview of the workflow to obtain the relative concentration ratios in the three phantom tubes. One instance of the PA forward model includes simulations of the light transport model, acoustic propagation and reconstruction for all N_{λ} wavelengths. For each tube k, the measured spectrum is fitted to the simulated spectrum using a linear scaling parameter β_k . The sum of differences between the spectra $\Delta \operatorname{Fit}_k$ is used to guide the parameter search (see Eq. 2 and 3). If the minimum sum of differences has been found, the concentration ratios in the tubes \mathbf{R}^* is estimated from the optical parameters { $\mu_{a,1}, \ldots, \mu_{a,k}$ } used to obtain the minimal sum of differences. If the minimum is not yet found, the concentrations are updated according to the coordinate search algorithm.

The PA spectra are computed by averaging the reconstructed pressure distribution $p_0^{sim}(\vec{r},\lambda)$ over all voxels belonging to a tube. This provides a mean PA signal $\bar{p}_0^{sim}(k,\lambda,\mu_{a,k})$ for tube k using a relative concentration of absorbers R_k , which yields $\mu_{a,k}$ according to Eq. 1. The experimental PA signal $\bar{p}_0^{exp}(k,\lambda)$ is averaged using the same voxels as to obtain \bar{p}_0^{sim} . In order to compare the modeled and measured spectra, the measured PA spectrum is fitted to the simulated one through least squares minimization using a scalar scaling (or calibration) factor β_k and the following error functional is used:

$$\Delta \operatorname{Fit}_{k}(R_{k}) = \sum_{i=1}^{N_{\lambda}} (\beta_{k} \cdot \overline{p}_{0}^{exp}(k, \lambda_{i}) - \overline{p}_{0}^{sim}(k, \lambda_{i}, R_{k}))^{2}.$$
(2)

In order to find the optimal parameters for all tubes, we use a coordinate descent algorithm,²⁰ where the relative concentration R_k in one tube represents one dimension. During the coordinate descent, the geometric parameters of the tubes and the optical properties of the background remain fixed. The only parameters that are being varied are the concentration parameters R_k for the three tubes, that determine the absorption coefficient $\mu_{a,k}$ (see Eq. 1).

The error landscape during the parameter search is determined by the sum of residuals (sum over all tubes):

$$E(\mathbf{R}) = \sum_{k=1}^{N_k=3} \Delta \text{Fit}_k(R_k), \qquad \mathbf{R} = (R_1, R_2, R_3)$$
(3)

During the parameter search, the concentration parameters R_k are updated for each tube iteratively and independently. In brief, the search is initialized using any (random) values for **R**. Furthermore, a direction v_k for each dimension k and a global step size h are initialized. As long as the error (Eq. 3) decreased, R_k is updated accordingly $R_k = R_k + v_k \cdot h$. The direction of the search is changed when the overall error E has increased. If the direction along the current dimension R_k has already been changed, the optimum along the next dimension is sought. If the minimum along all three dimensions has been found with the current step size h, h is decreased (e.g. by a factor 2) and the search continues with the first tube, thereby trying to find the R_k that minimizes the difference between PA spectra for the first tube (Eq. 2). As stop criterion we used the total number of steps and whether a minimum step size has been reached. The values of **R** during the search are used to avoid multiple visits of the same location in the parameter space. If a location has been visited, another location in the same direction is sampled, while staying within the boundaries of $R_k = (0, 1)$. The progress during and the results of the parameter search is shown in section 2.3 and Fig. 8.

2.4 Evaluation of Monte-Carlo light model

An important prerequisite in qPAT is the validation of methods underlying the quantification of chromophore concentrations. In a model-based approach, this involves answering the question which model parameters influence the solution that is being compared to measured data. When using MC simulations, naturally only a limited volume can be simulated in order to gain the solution within the region of interest (ROI). However, this choice regarding the position of the boundaries, i.e. how large the simulated volume is or how far the boundaries are situated from the ROI, can affect the solution within the ROI.

Here, in preparation for the quantitative estimation of concentration ratios, we address two important issues concerning the setup of the MC light model simulations: First, we study the question as to how large the simulated volume needs to be in order to exclude boundary effects on the fluence distribution inside the ROI, representing the size of measured PA images. Second, the effect of absorbers in the background (outside the ROI) on the solution within the ROI is investigated.

The first question is addressed by simulating a phantom model using varying volume sizes while keeping the phantom model (i.e. the ROI) in the center of the simulated volume. The phantom consists of multiple tubes arranged in a grid of four layers with optical parameters very similar to the one used for the comparison of experimental data and the parameter estimation (see Table 1). A schematic of the setting is shown in Fig. 4 A, B, C.

The region of interest was defined as a cube with an edge length of 20 mm corresponding to the imaged volume size in the PA measurements. The simulated volume was increased in several steps to a maximum size of 50^3 mm^3 , and the fluence distribution inside the tubes (averaged over the tube's cross section) was used as a measure to test convergence (see Fig. 4 D). We observed that the influence of the boundary condition on the fluence distribution inside the tubes is stronger with increasing depth. This is due to the fact that the fluence at greater depths is strongly determined by scattered light and photons that have interacted with the volume boundary if the boundary is close to the ROI. Hence, the fluence distribution inside a tube in the deepest layer was used as measure to test convergence (indicated by the yellow cross in Fig. 4 B). We found that convergence within the region of interest (ROI) was achieved by adding a boundary region that approximately doubled the total volume of the model (see Fig. 4, D). Consequently, the MC model in the inversion (section 3) included an additional boundary region in order to exclude these boundary effects due to limited volume size. The boundary region had identical optical parameters as the background inside the ROI.

The second question, the effect of background absorbers on the fluence distribution within the ROI, was addressed by comparing two settings, shown in Fig. 5 A. In one setting, the grid of absorbing tubes extended into the additional boundary region, in the other setting the tubes were truncated and remained inside the ROI. Again, we compared the fluence distribution in a tube at a depth of 7 mm averaged over the tube's cross section to study the influence of the background. The result is shown in Fig. 5 B. In the case with truncated tubes, the fluence shows a strong increase near the ROI boundaries which extends even into the ROI, compared to the setting with continuous tubes. This effect is due to the light scattered in the additional boundary region, which acts as a light source leading to an increased absorption at the endings of the truncated tubes. In contrast, in the setting with continuous tubes, there is no sharp transition between strongly absorbing and weakly absorbing materials. In this setting, photons are absorbed by the continuous tubes when leaving the ROI. This leads to a difference in the fluence distribution between the two settings and shows that absorbers outside the ROI do affect the solution within the ROI.



Figure 4: MC light model validation. A: Front view of the experimental setting used for the MC light model evaluation. The profile of the excitation beam is shown in yellow and red (yellow representing high intensity). The parts of the tubes lying within the ROI are colored in blue. Tube parts extending outside the ROI are shown in green. The maximum dimensions of the simulated volume is $500 \times 500 \times 500$ voxel, or 50^3 mm³ B: Phantom setting viewed from above. The dimensions of the ROI is $200 \times 200 \times 200$ voxel, or 20^3 mm³. The yellow cross indicates the tube whose fluence distribution is shown in D. C: Distinction between ROI and background volume for the same perspective as in B. D: Effect of boundary conditions on fluence within one tube at a depth of 7 mm indicated by the yellow cross in B. The fluence is shown along the tube axis averaged over the tube cross section of one central tube. The ROI is depicted in gray. The differently colored curves represent results using different surrounding volumes, where Nx = 200 means that no additional surrounding volume has been used.

3. RESULTS

3.1 Comparison of experimental data with model

For a qualitative validation of the PA forward model, the measured and modeled reconstructed initial pressure distributions $p_0^{exp}(\vec{r}, \lambda)$ and $p_0^{sim}(\vec{r}, \lambda)$ are compared. For this purpose, we used the known optical properties for



Figure 5: Effect of background absorbers. A: Truncated (top) and continuous tubes (bottom) B: Fluence within a tube averaged over cross section for the two settings shown in A.

the tubes and for the scattering background material (see Table 1) in the two-stage PA model. A comparison of the measured data, the MC light model output, and the modeled PA image is shown in Fig. 6. A slice in the center of the volume orthogonal to the tube axes shows that the PA image reproduces the limited aperture artifacts (see Fig. 6 A, C). This also becomes visible in horizontal profiles seen in Fig. 6 D, showing data along a line of voxels in the center of the volume, orthogonal to the tube axes and the excitation beam direction (indicated by the horizontal line in Fig. 6 A-C). It can be seen that the PA image does not capture all artifacts (negative p_0 values) that are visible in the measured data p_0^{exp} . The reason for the missing artifacts are likely acoustic inhomogeneities²¹ or the interaction between pressure waves and the FPI detector, which are not modeled by the acoustic propagation model. Still, the artifacts visible along the excitation beam direction (z-axis) shown in Fig. 6 E are well reproduced in the PA image. The curves shown in Fig. 6 D-F have been normalized to their respective maximum. Thus, the two-stage PA forward model shows good qualitative agreement with the measured data.

In order to compare the PA forward model to measured data in a quantitative way, we compare the PA spectra obtained through averaging the $p_0^{exp}(\vec{r}, \lambda)$ and $p_0^{sim}(\vec{r}, \lambda)$ over all voxel belonging to the tubes. The PA spectra \overline{p}_0^{exp} and \overline{p}_0^{sim} were measured and simulated using seven wavelengths between 614 nm and 930 nm. As the FPI detects pressure signals using voltage signals from a photodiode, a quantitative comparison requires a calibration or scaling factor between modeled and measured pressure values. This calibration factor was obtained by fitting the measured PA spectra to the modeled spectra using the least squared method with a scalar factor, see Eq. 2. A comparison of the measured and predicted PA spectra for all three tubes is shown in Fig. 7.

3.2 Parameter estimation

The aim of the parameter estimation is to determine the concentration parameter R_k for all three tubes k = 1, 2, 3 (see Eq. 1) representing the relative concentration of NiSO4 and determining the optical properties of the tubes. For this purpose, the PA spectra from simulations and measurements were compared using a least squares fit between the two as described in section 2.3. The objective function E as given by Eq. 3 is sampled iteratively by simulating one PA spectrum (comprising seven wavelengths) at a time using the MC light model. The value of **R** (and thereby the $\mu_{a,k}$) are updated after each iteration depending on the previous search and how the value



Figure 6: Measured and modeled PA images and intensity profiles: A: Measured cross sectional PA image of the phantom, B: Initial pressure distribution obtained using the MC model, C: Cross sectional PA image predicted using the forward model, D: Image intensity profiles corresponding to the dashed horizontal lines in A)-C), E: Image intensity profiles corresponding to dash-dot lines in A)-C), F: Image intensity profile of along a tube in x-direction averaged over the tube cross section.

of E has changed. The objective function E is a three dimensional function where each dimension represents the concentration parameter R_k for one tube. A one- and two-dimensional representation of E is shown in Fig. 8 A and B, respectively. The two-dimensional error landscape in Fig. 8 B has been interpolated using cubic interpolation based on 11×11 evenly spaced samples for the two parameter R_1 and R_3 . The progress of the coordinate descent is shown in Fig. 8 B and C. In Fig. 8 B, the parameter search is initialized with $\mathbf{R} = 0$, which is indicated by the black cross at $R_{1,2} = (0,0)$. There, sampled values of the parameter space are indicated by crosses with the gray value representing the progress, where black represents the beginning, gray indicate intermediate samples and white represents the final convergence of the search. The real concentration is indicated by the yellow diamond at (0.766, 0.273), and the final values are represented by the white cross in Fig. 8 B. In the course of the parameter search, the error measure E (evaluated with the currently best values of \mathbf{R}) is decreasing monotonously, as shown in Fig. 8 C.

A comparison of the values obtained by the coordinate descent parameter search and the real values is given in Table 2.

Table 2: Estimated relative concentrations. Results have been obtained running a coordinate search where the relative NiSO4 concentration in one tube represents one dimension.

	Relative NiSO4 concentration			
	Tube 1	Tube 2	Tube 3	
Estimated concentration \mathbf{R}^*	79.7 %	56.2~%	29.0~%	
Known concentration	76.6~%	51.7~%	27.3~%	



Figure 7: Measured and predicted PA spectra: PA image intensity was averaged over the respective tube volumes. The spectra were fitted using least-squares with a linear scaling factor. Dashed lines indicate the measured spectra, solid lines indicate simulated spectra. The blue curves correspond to tube 1, which contains 76.6 % NiSO4; the red curves correspond to tube 2 with 51.7 % NiSO4; the black curves correspond to tube 3 with 27.3 % NiSO4.

4. DISCUSSION

In this study, we presented a model-based inversion scheme for the estimation of absorber concentration ratios. The model comprises a two stage approach with a MC light transport model and acoustic propagation model. The MC light model has been evaluated with respect to boundary conditions and background absorbers. It has been found that background absorbers influence the solution of the fluence inside the region of interest. The parameter estimation was based on the comparison between measured and modeled PA spectra and a coordinate descent parameter search with decreasing step size. The parameter search yielded an agreement between estimated and known concentration values within 5%. The remaining difference arises from the minor mismatch in the PA spectra, which is likely due to an incomplete representation of the experimental setting in the PA model. In addition, effects of different Grüneisen parameters for different tubes could have contributed to the mismatch. Furthermore, in the PA model presented here, acoustic absorption²² and attenuation were not considered. These factors, as well as acoustic heterogeneities,²¹ which were not included in the model, could explain the remaining mismatch between measured and modeled data and the incomplete representation of artifacts that has been observed.

Despite the promising results obtained with the parameter estimation framework presented here, further work is required to retrieve the absolute concentration of absorbers, which is an important issue for future research. A limitation of the presented approach is based on the image segmentation employed here, which requires prior knowledge regarding absorber geometries, which is not known for more complex settings including data obtained from tissue. Nevertheless, our aim was not to provide a general solution for image segmentation problems occurring in PAT, but rather to present an initial proof-of-concept that reducing the number of unknowns using image segmentation and thereby allowing the use of a gradient-free parameter search.

The parameter estimation approach presented here is based on the fact that the MC light model does not



Figure 8: Concentration estimation using coordinate search. Parameters are updated according to the difference between measured and modelled PA spectra using the error measure $\sum_k \Delta \operatorname{Fit}_k$. A Error measure as a function of c_{NiSO4} in tube 1, all other parameters fixed (indicated by white dotted line in B). B Error landscape and parameter search using the relative concentration of NiSO4 in tubes 1 and 3. Blue color in the error landscape represent low values, red color indicates high values of E. Crosses indicate evaluations during the search. The progress of the search (iteration number) is represented by the gray values of the crosses (from black=start to white=finish). C Error measure versus iteration count. The y-axis represents the error measure as defined in Eq. 3 on a logarithmic scale. The search has been stopped after reaching a maximum number of iterations.

provide an analytical access to gradients of the objective function. This requires the parameter space, i.e. the absorber concentrations, to be sampled iteratively. This, however, becomes computationally expensive when the number of parameters or unknowns is increased. Hence, the presented framework is likely limited to situations in which the number of parameters is not significantly larger than ten. For problems with higher dimensions, a gradient-based approach becomes inevitable. In this context, the use of adjoint models^{23–25} rather than pure MC-based methods may be an alternative approach to overcome this limitation.

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