Robust inference of baseline optical properties of the human head with three-dimensional segmentation from magnetic resonance imaging

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We model the capability of a small (6-optode) time-resolved diffuse optical tomography (DOT) system to infer baseline absorption and reduced scattering coefficients of the tissues of the human head (scalp, skull, and brain). Our heterogeneous three-dimensional diffusion forward model uses tissue geometry from segmented magnetic resonance (MR) data. Handling the inverse problem by use of Bayesian inference and introducing a realistic noise model, we predict coefficient error bars in terms of detected photon number and assumed model error. We demonstrate the large improvement that a MR-segmented model can provide: 2–10% error in brain coefficients for $2 \times 10^6$ photons, 5% model error. We sample from the exact posterior and show robustness to numerical model error. This opens up the possibility of simultaneous DOT and MR for quantitative cortically constrained functional neuroimaging.

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1. Introduction

Diffuse optical tomography (DOT) is arousing growing interest as a noninvasive tool for neuroimaging, both clinical and functional, as well as other clinical applications such as breast tumor detection and tracking muscular oxygenation, and arthritic joint imaging. By use of spectroscopy, this modality can couple directly to hemodynamic quantities of interest, measuring both total hemoglobin concentration and oxygenation. Optical contrast can also arise from cell-based mechanisms such as the redox state of cytochrome-c-oxidase and in vivo contrast agents such as fluorescent and voltage-sensitive dyes. By relying on photon transport through tissue, DOT also accesses spatial information to a depth of several centimeters. DOT shows great promise for functional neuroimaging: The advantages of functional DOT (fDOT) include fast temporal resolution of the order of 10 ms and moderate spatial resolution of the order of 1–2 cm, placing it in these two categories somewhere between both MEG (magnetoencephalography) and EEG (electroencephalography), and functional magnetic resonance imaging. In addition to sensitivity to absorbing chromophores, DOT can be sensitive to cellular scattering changes during neuronal activation. DOT is noninvasive and nonionizing. The apparatus is relatively inexpensive, is compatible with (and complementary to) other modalities allowing simultaneous imaging, is portable, is capable of continuous monitoring, and does not require an immobile subject.

The key challenge of DOT is that of extracting spatial maps of the optical properties (absorption coefficient $\mu_a$ and reduced scattering coefficient $\mu_s'$) within a highly scattering tissue volume by coupling multiple light sources and multiple detectors to the surface of the skin. The available signals comprise light intensities at each detector that are due to each source. For each of these source–detector pairs, it is possible to measure a dc intensity (continuous-wave systems), or intensity amplitude and phase (rf-modulated systems), or obtain the intensity distribution as a function of time of flight (time-domain systems). Because tissue dimensions of interest are much larger than the photon mean free path, the path taken by photons from source to detector is dif-
fusive rather than straight; this is what limits the spatial resolution of DOT. Recovery of $\mu_a(r)$ and $\mu_s'(r)$ from measured signals requires the solving of an inverse problem, nonlinear in the optical parameters, and known to be ill-posed.\textsuperscript{15,16} Usually $\mu_s'(r)$ is measured at several wavelengths within the near-infrared low-tissue-absorption window of 650–900 nm. From this, the known spectral absorption curves\textsuperscript{17} of the chromophores HbR and HbO\textsubscript{2} allow spatial maps of [HbR] and [HbO\textsubscript{2}] (and therefore of total hemoglobin concentration) to be constructed.

Our goal in this paper is to explore the limits of accuracy in the measurement of baseline optical properties of the human head using a time-domain apparatus when high-resolution anatomical information from magnetic resonance (MR) is used to constrain the optical model. Absolute cerebral oximetry and blood volume measurement, which require baseline (absolute) quantification of cortical $\mu_a$, are important for the study of stroke,\textsuperscript{18} head trauma, migraine, neonatal ischemia,\textsuperscript{19} and brain development.\textsuperscript{20} Baseline properties are important for another reason. For DOT it is common to use a perturbation model where signal changes are taken to be a linear function of optical parameters. This allows rapid imaging by matrix inverse methods.\textsuperscript{15,21–23} However, one cannot\textsuperscript{24} compute the required sensitivity functions without knowing both baseline (absolute) $\mu_a$ and $\mu_s'. We envisage using simultaneous MR and DOT to perform accurate baseline measurements, followed by cotrictedally constrained fDOT imaging and simultaneous and BOLD (blood oxygenation level dependent) fMRI.\textsuperscript{3,14}

In our model the scalp, skull, brain, and cerebrospinal fluid (CSF) are assigned separate optical properties, assumed uniform within each tissue type, and their three-dimensional (3-D) geometry is taken from automatically segmented MR images. This greatly reduces $N$ the number of unknowns (we use $N = 6$, compared with $N \sim 10^2$–$10^4$ that is common in pixel- or voxel-based representations), making the inverse problem much more tractable. This idea of MR-constrained reconstruction is new to DOT,\textsuperscript{25} certainly in two dimensions,\textsuperscript{26,27} nor to other medical inverse problems.\textsuperscript{28,29} Note that our approach differs from the class of segmentation methods in which tissue boundaries are themselves parameterized by unknowns.\textsuperscript{30,31}

Time-resolved intensity measurement is popular to extract baseline properties in simple homogeneous\textsuperscript{32–34} and layered\textsuperscript{35–38} slab tissue models, in both transmission and reflection geometries. Time-of-flight information resolves otherwise indistinguishable effects of absorption and scattering changes.\textsuperscript{15} For example, Kienle and Glanzmann\textsuperscript{39} use a two-layer analytic diffusion model to fit for optical coefficients of in vivo arm muscle, with the superficial fat layer thickness constrained by another imaging modality (in this case ultrasound). For the adult head, in vivo measurements also have usually been analyzed with simple analytical diffusion models, even though the internal geometry may be poorly represented as a slab or layered slab.

To overcome these limitations, we use a numerical forward model that can handle arbitrary 3-D tissue geometries and optical locations in the diffusion approximation. We use this to perform model-based fitting by nonlinear optimization.\textsuperscript{15,40,41} We use the Bayesian paradigm for inference, giving us the full posterior probability density function (PDF) of the parameters (which in turn could be used to obtain the full PDF of baseline [HbR] and [HbO\textsubscript{2}]). Bayesian inference has been used with success in related medical inverse problems.\textsuperscript{39,42–44} However, fully Bayesian\textsuperscript{41,45,46} or Bayes-influenced\textsuperscript{47} applications in DOT are less common. In contrast to most previous research, we use the posterior PDF to study expected errors (i.e., error bars) and the detailed distribution in the parameters rather than presenting a single best solution. We also introduce a novel realistic noise model that captures our belief in signal reliability at both small and large numbers of detected photons. This accounts for photon detection noise and forward modeling errors; the latter have been ignored in the Bayesian DOT literature thus far.

This paper is organized as follows. In Section 2 we outline the application of Bayesian inference to our problem and introduce the general form of the likelihood function. In Section 3 we present the head system and the forward and noise models used for inference and simulation of noisy experimental signals. In Section 4 we give results showing the accuracy of inference achievable using a homogeneous head model and a segmented head model. We present achievable error bars as a function of total collected photons and assumed model errors. We investigate in detail the posterior distribution in the optical parameters using a PDF sampling method and validate our choice of posterior approximation. We also demonstrate robustness to forward model errors. We conclude and suggest future directions in Section 5. Two appendices contain methodological details that would otherwise impede the flow of the main text.

2. Inference Framework

The Bayesian approach treats an inverse problem as an inference problem: Our lack of knowledge about model parameters is represented by a PDF over those parameters. A model represented by $H$ (for hypothesis) contains unknown parameters given by the vector $x = \{x_1 \ldots x_N\}$ and includes a prior PDF on those parameters $p(x|\mathcal{H})$. We consider how this PDF is modified by the arrival of the experimental data (measured signal) vector $y = \{y_1 \ldots y_M\}$ to give a posterior PDF:

$$p(x|y, \mathcal{H}) \propto p(y|x, \mathcal{H})p(x|\mathcal{H}),$$  \hspace{1cm} (1)

where $p(y|x, \mathcal{H})$ is the likelihood defined by model $\mathcal{H}$, and the constant of proportionality depends only on $y$. The posterior encodes everything we now know about $x$. When we are not distinguishing between different models, we drop the conditionality on $\mathcal{H}$ in our notation.
The relevant advantages of this framework include the following: (1) Explicit formulation of all assumptions that are present in all approaches to inverse problems but are not always expressed. (2) The ill-posed nature of the inverse problem, implying uncertainty in some parameter directions, is embraced and handled probabilistically. This contrasts with traditional approaches where this is viewed as ‘instability’ and is therefore removed by ad hoc regularization methods. (3) The posterior PDF contains all confidence intervals and error correlations of parameters. In the case of hemoglobin concentration parameters, their posterior could be used to infer neural activation (with fitting models of neural-hemoglobin coupling) with more reliability than best-fit parameter values alone. (4) Probabilistic prior information, for example, from another imaging method, can be consistently made use of, allowing optimal use of multimodal imaging information. (5) The Bayesian method is optimal in the sense of giving unbiased minimum-variance estimators when the likelihood and prior are correct. (6) Complex models (with many additional, or hidden, parameters such as amplitude calibrations) can be handled without the danger of overfitting that can occur with simple cost-function minimization. (7) Competing models can be ranked by their ability to explain the data, even if they have different structure and numbers of parameters. Offsetting these advantages is the main obstacle to use of Bayesian methods: They can be computationally intensive compared with more ad hoc approaches. For an introduction, see the informal tutorial by MacKay or other more detailed reviews.

We take a forward model \( f(x) \) that encapsulates our physical model of the DOT system. Given an optical parameter vector \( x \), it returns the expected signal vector \( f = (f_1 \ldots f_M) \). We also need a noise model, giving the probability that a signal \( y \) could be generated by the addition of noise to the noise-free signal \( f \). We use an independent Gaussian noise model, giving the likelihood function

\[
p(y|x) \propto \exp[-L(y; x)],
\]

with the negative log likelihood

\[
L(y; x) = \frac{1}{2} \sum_{m=1}^{M} \ln \sigma_m^2 + \frac{1}{2} \sum_{m=1}^{M} \frac{(f_m(x) - y_m)^2}{\sigma_m^2}.
\]

Each noise standard deviation \( \sigma_m = \sigma[f_m(x)] \) is given by the same function applied to the corresponding signal level \( f_m(x) \). The form of \( \sigma(f) \) is discussed in Subsection 3.D. The second term is analogous to a \( \chi^2 \) cost function. The constant of proportionality and the log term arise from the normalization requirement \( \int \sigma^M p(y|x) = 1 \). Our inference procedure is shown schematically in Fig. 1.

For this study we used a constant prior \( p(x) \) within certain biologically motivated bounds on each parameter \( x_n \in [x_{n,\text{min}}, x_{n,\text{max}}] \) and zero outside (in other words, a standard minimum–maximum prior). This reflects a lack of preference over \( x \) within these bounds and zero belief in values outside the bounds. Therefore the posterior is

\[
p(x|y) \propto \begin{cases} 
\exp[-L(y; x)] & x_n \in (x_{n,\text{min}}, x_{n,\text{max}}) \forall n, \\
0 & \text{otherwise}
\end{cases}
\]

where we do not need to know the constant of proportionality. It would be simple to encode more specific prior beliefs than this simple constraint.

For \( N \) more that 2 or 3, the high dimensionality and the fact that each evaluation of \( f(x) \) requires a time-consuming solution of a PDF make it impossible in general to characterize the posterior over all \( x \). However, for differentiable \( f(x) \), there will always be a sufficiently small choice of \( \sigma(f) \) that the bulk of the posterior probability mass will be close to the maximum a posteriori (MAP) value \( x_{\text{MAP}} \) and will be well approximated by a multivariate Gaussian with covariance matrix \( \Sigma_{\text{MAP}} \) and mean \( x_{\text{MAP}} \). The inference task is then to locate \( x_{\text{MAP}} \) and measure \( \Sigma_{\text{MAP}} \), from which confidence intervals on each \( x_n \) can be computed. In all but Subsection 4.D we use this approach; details are presented in Appendix A.

We note that this search for \( x_{\text{MAP}} \) is analogous to model-based approaches where an objective function (cost function) \( L(y; x) \), in our case differing from the weighted least-squares form only by an additional log term, is minimized by an iterative approach. Indeed much of the machinery is in common. However, the interpretation is different: Those who use model-based approaches are generally interested in the single best solution rather than properties of the full posterior PDF. (Often this restriction is a practical one because of large \( N \).)

When the posterior is significant over a region where \( f(x) \) is no longer linearizable, the Gaussian approximation becomes bad. In this case we use Markov chain Monte Carlo (MCMC) sampling to
generate a set of uncorrelated samples from the exact posterior, providing a (noisy) cloudlike impression of the full PDF. We demonstrate this more general but computationally intensive method in Subsection 4.D.

3. Forward and Noise Model

A. Head System

We start with a human head segmentation geometry obtained at a 1 mm by 1 mm by 1.5 mm voxel resolution from a MR structural image using the technique of Dale et al..\textsuperscript{59} This data consist of an assignment of each voxel to one of the five categories: scalp, skull, CSF, brain, or not tissue (air). (We did not distinguish between gray and white matter; gray matter will dominate the optical properties because of the rapid decay of sensitivity with depth.) For the subject data used, the scalp and skull thicknesses were typical, being 5–7 and 7–8 mm, respectively, in the relevant region of the head. Figure 2 shows our head geometry. Unless otherwise stated, we use as our standard optical properties for the four tissue types the values given in Table 1. These are believed to be typical, falling within the quite wide variation of published values.\textsuperscript{53,60,61}

The CSF falls into a special category. It is presumed to be approximately $10^2$ times less scattering and less absorbing than other tissue types and occupies a much smaller volume. Its structure is convoluted and uneven, varying from a thin layer of approximately 1–2 mm thickness hugging the dura, to folds and pockets of several millimeters in thickness and size, following the folds of the brain surface.\textsuperscript{62} Once the CSF geometry is held fixed, realistic biological variation in either CSF $\mu_a$ or $\mu_a'$ causes negligible changes in the photon transport, and hence detected signals. For $\mu_s$, this is because the values and volume are too small to cause any significant absorption of light compared with that caused by surrounding tissues.

For $\mu_a'$, the reason is subtly different: The extremely long reduced scattering length of $1/\mu_a' \approx 100$ mm is much longer (by a factor of the order of 5) than maximal line-of-sight distances within the CSF void region. This is mainly due to the folded and irregular geometry and is most likely enhanced by surface roughness\textsuperscript{63} and the presence of vasculature in the CSF below the MR resolution. Thus typical free transport distances in the CSF are dominated by the length scale of the irregular folds and vessels. We believe that photons in the CSF pass into other highly scattering tissue types long before the particular value of $\mu_a'$ becomes relevant.

Therefore we do not try to infer CSF properties in our segmented model, and our unknowns will consist of $\mu_a$ and $\mu_a'$ for the remaining three tissues. We compare two models:

- $\mathcal{H}_{\text{hom}}$: The interior of the head is assumed homogeneous, with $N = 2$ unknown parameters $\mu_{a,\text{hom}}$ and $\mu_{s,\text{hom}}$ describing a single tissue type.
- $\mathcal{H}_{\text{seg}}$: The interior of the head is segmented as described above, with $N = 6$ unknown parameters $\mu_{a,\text{scalp}}$, $\mu_{s,\text{scalp}}$, $\mu_{a,\text{skull}}$, $\mu_{s,\text{skull}}$, $\mu_{a,\text{brain}}$, and $\mu_{s,\text{brain}}$. Note that the CSF is present in this model but has fixed parameters.

The unknown (or fitting) parameters were given bounds $[x_{n,\text{min}}, x_{n,\text{max}}]$ of [0.004, 0.04] mm$^{-1}$ for all absorption and [0.4, 4.0] mm$^{-1}$ for all reduced scattering coefficients.

B. Optodes and Detection Model

We chose to model a two-source ($N_s = 2$) and four-detector ($N_d = 4$) fiber-coupled time-resolved system contacting a small region of the scalp at the top of the head. The arrangement, shown in Fig. 2, was chosen to cover a range of source–detector distances of 10–36 mm. We assume that the system counts photons and bins these counts according to their arrival time, building up a histogram of the temporal point-spread function (TPSF). We assume no convolution of the TPSF because of the measurement system (i.e., instrument response function), but this would be easy to include in the forward model.

For simplicity, we assume that optode locations are known accurately and that the system has been calibrated to provide absolute measurements of amplitude and of time of flight. (We do not model the

![Fig. 2. Simulated optode arrangement and placement on the head (the face, pointing downward, is mostly hidden). 3-D MR-segmented head geometry is exposed by a sagittal slice. The tissue-type color coding on this slice is, from lightest to darkest, scalp, skull, CSF, brain.](image-url)
variable attenuation that is often used\textsuperscript{7,64} to prevent detector saturation at small optode separations.)

One TPSF is available for each of the \( N_x \times N_y = 8 \) source–detector pairs. We represent each TPSF by 18 numbers, giving the photons collected in each of the 100-ps-wide time gates in the time-of-flight range 0.2–2.0 ns. We found that for time of flights below 0.2 ns, diffusion forward model errors were too large to be useful.\textsuperscript{65} Beyond 2.0 ns, the signals generally fall below the 1-photon level. An example simulated signal vector \( \mathbf{y} \) is shown in Fig. 3. Note that our signals are presented in units of detected photons.

C. Diffusion Forward Model

Photon transport in scattering media at macroscopic scales, where interference effects can be ignored, is described by the transport equation.\textsuperscript{15,66} In media where \( \mu_s << \mu_a \) and length scales of interest are much larger than \( 1/\mu_s \), transport can be well described\textsuperscript{15} by the diffusion approximation (DA):

\[
\frac{1}{v} \frac{\partial}{\partial t} \phi = \nabla \cdot (\kappa \nabla \phi) - \mu_a \phi + q,
\]  

(5)

where \( \phi(\mathbf{r}, t) \) is the fluence, \( q(\mathbf{r}, t) \) is the source term, \( \kappa(\mathbf{r}) \) is the local diffusion constant, \( \mu(\mathbf{r}) \) is the local absorption, and \( v(\mathbf{r}) \) is the local speed of light in the medium. We use the good approximation\textsuperscript{67,68} \( \kappa = 1/(3\mu_s) \) and assume \( v(\mathbf{r}) = c \) everywhere corresponding to unity refractive index. Our segmented map of \( \mu_s \) is given when we assign \( \mu_s(\mathbf{r}) = \mu_{s,\text{tissue}}(\mathbf{r}) \) where tissue(\( \mathbf{r} \)) represents the tissue type of the voxel within which \( \mathbf{r} \) falls. Note that the resulting discontinuities in optical properties can cause discontinuities in \( \nabla \phi \), but not in the value of \( \phi \) itself (this would not be the case had we allowed refractive-index changes). For tissue–air boundary conditions we found the Dirichlet (\( \phi = 0 \)) approximation to be sufficiently close to the more accurate Robin boundary condition\textsuperscript{15} because \( \kappa \) is much smaller than the thicknesses of interest.

We use a finite-difference time-domain (FDTD)\textsuperscript{69} method to compute the evolution of Eq. (5), from which the signal expectation vector \( \mathbf{f}(\mathbf{x}) \) is extracted by use of the detector locations. Details are given in Appendix B. The method represents the smooth function \( \phi(\mathbf{r}, t) \) as discrete values on a cubical lattice of nodes, at a sequence of time steps. We resample the segmentation voxel map to the required lattice resolution, in this study either 2 or 1 mm. For a 2-mm voxel size, with \( 3.3 \times 10^6 \) nodes in the required head volume, our current FDTD method takes approximately 8 s/source (on a 1-GHz CPU) to simulate 2 ns of propagation time. We did not optimize the forward model, and there exist refinements of FDTD that can be much faster (see Appendix B). Typical error sizes at 2 mm can be judged from Fig. 9 (keep in mind that these signals span close to 6 orders of magnitude).

A note is necessary to explain how we treat the CSF. In recent years, research has been done that shows the large fluence errors that can result when the extremely low \( \mu_s' \) value in voidlike regions is fed directly into the DA.\textsuperscript{67} (These errors were measured by comparison with transport equation solutions.) We chose a different tactic, similar to that of Ripoll \textit{et al.}\textsuperscript{63} By giving the CSF an effective \( \mu_s' \) for use within the DA, we were able to approximate the physics much better than possible using the true \( \mu_s' \). As discussed in Subsection 3.A, line-of-sight distances in the CSF are small, we believe of the order of \( l \sim 10 \) mm because of highly irregular geometry and vasculature. We believe that the optimal DA choice (which may vary from subject to subject) is a \( \mu_s' \) of the order of \( l^{-1} \). Our preliminary results suggest that the fluence field is not sensitive to the exact \( \mu_s' \) chosen when the full 3-D MR head geometry is modeled. In contrast, most previous comparisons have used idealized two-dimensional CSF geometries with long lines of sight\textsuperscript{60,67,70} or two-dimensional models taken from a single MR slice.\textsuperscript{67} In this paper we fix \( \mu_s',\text{CSF} = 0.4 \) mm\(^{-1}\). The largeness of this choice is in part influenced by numerical efficiency: The CPU time for our current FDTD scales inversely with the smallest \( \mu_s' \) in the system, which is always \( \mu_{s,\text{CSF}}' \) in our case.

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D. Noise Model for Inference

The forward model provides the signal expectation value vector \( \mathbf{f}(\mathbf{x}) \). Bayesian inverse methods always require a noise model, which captures our uncertainties about the difference between the numerically generated \( \mathbf{f}(\mathbf{x}) \) and the real-world signals \( \mathbf{y} \), given that the parameters \( \mathbf{x} \) were actually correct.

Recall that in Eq. (3) we assigned Gaussian distributions to each of the components \( m = 1 \ldots M \) independently, each with a mean \( f_m \) and a standard deviation \( \sigma(f_m) \). The Gaussian approximation to the Poisson photon detection statistics\(^{31} \) would yield \( \sigma^2(f) = f \). Remember that signal units are in (effective) photons per time gate. This approximation is good for \( f \gg 1 \), becoming bad (especially in the tails) as \( f \) approaches 1. To handle sensibly the case \( f < 1 \), we place a lower limit of 1 on \( \sigma \). (This limit could be increased to account for additive electronic noise.)

However, there is a problem at large signals: If some \( f_m \) is, say, \( 10^6 \), giving \( \sigma_m = 10^3 \), then we cannot be expected to believe that the fractional error \( \sigma_m/f_m \), and therefore our trust in our forward model’s closeness to reality, is 0.1%. Rather we choose a fraction \( \epsilon \) that is a lower limit on our fractional error and takes account of

- (1) modeling of physics of photon migration in a given tissue geometry (e.g., transport corrections to the DA);
- (2) deviations from the assumption of uniform optical properties within a given tissue type;
- (3) incorrect tissue-type assignments from automatic MR segmentation; and
- (4) the accuracy with which absolute amplitude (and time offset) calibration can be carried out, including effects of optode–skin coupling variations that are due to, e.g., skin pigmentation.

We typically choose \( \epsilon = 0.05–0.2 \), corresponding to a 5%–20% model and calibration error.

Combining the above, the noise level \( \sigma(f) \) is a piecewise power law:

\[
\sigma(f) = \begin{cases} 
1, & f \leq 1 \\
 f^{1/2}, & 1 < f \leq 1/\epsilon^2 \\
 \epsilon f, & f > 1/\epsilon^2 
\end{cases}
\]  

(6)

This is shown by the solid line in Fig. 3(b). Typically the peaks in \( f \) are fractional-error dominated, whereas the tails are Poisson statistics dominated.

E. Simulating Experimental Signals

In this proof-of-concept study, we generate simulated experimental signals using numerical forward models of the same type as used for the inference (inverse) problem. Given a true optical parameter vector \( \mathbf{x}^{(0)} \), we generate a noise-free signal expectation vector \( \mathbf{f}(\mathbf{x}^{(0)}) \), to which we apply a simulated noise model.

Our simulated noise is identical to our inference noise (as described in Subsection 3.D), except it includes only the detection noise component. We do not explicitly add noise to simulate model error; rather in Subsection 4.E we investigate the effects of model error by changing the forward model used to calculate \( \mathbf{f}(\mathbf{x}^{(0)}) \). This yields the simulated noise level

\[
\sigma_{\text{sim}}(f) = \begin{cases} 
1, & f \leq 1 \\
 f^{1/2}, & f > 1 
\end{cases}
\]  

(7)

This is shown by the dashed–dotted line in Fig. 3(b). Note that the difference between simulated and inference noise models manifests itself in Fig. 3(d) as a residual \( \beta_m \) [see Eq. (A3)], which has a variance \( \ll 1 \) for the \( m \) values where \( f_m \gg 1/\epsilon^2 \).

The recipe to simulate experimental signals is

\[
y_m = \max\{f_m(\mathbf{x}_b) + n_m, 0\}, \quad m = 1 \ldots M, \quad (8)
\]

where each \( n_m \) is independently sampled from a univariate Gaussian distribution with zero mean and variance \( \sigma_{\text{sim}}^2(f_m(\mathbf{x}_b)) \). The maximum value operation removes unphysical negative signals.

4. Results and Discussion

A. Homogeneous versus Segmented Head Fit

We are interested in finding out what improvement is possible in fitting baseline optical parameters when anatomical segmentation information becomes available. Therefore in this subsection we compare the models \( \mathcal{H}_{\text{hom}} \) and \( \mathcal{H}_{\text{seg}} \) in their ability to infer these parameters, using simulated data also generated from \( \mathcal{H}_{\text{hom}} \) or \( \mathcal{H}_{\text{seg}} \). We choose a total detected photon number (which includes both sources)

\[
N_p = \sum_{m=1}^{M} y_m \quad (9)
\]

at approximately \( 2 \times 10^6 \), typical for photon-counting DOT systems. As we vary the head optical properties, we decided to hold the collection time constant rather than fix \( N_p \). Note that some advantage, in terms of smaller \( N_p \) values, could be gained if variable detector attenuation\(^{44} \) were used. (Figure captions 4–7 and 10 give the \( N_p \) range for each experiment.) In this subsection we fix \( \epsilon = 0.05 \) and use a 2-mm forward model lattice. Recall that all simulated signals include realistic detection noise.

1. Homogeneous–Homogeneous Fit

Using signals from \( \mathcal{H}_{\text{hom}} \), we fit using \( \mathcal{H}_{\text{hom}} \) and sweep the true optical parameters. The results are presented in Fig. 4. This shows that if the head were indeed homogeneous, then accurate inference of its baseline optical parameters would be possible. The error bars (representing the expected measurement error of the parameters) are 0.5% or less. The true values fall within, or just outside, the error bars.

2. Segmented–Homogeneous Fit

Using signals from the more realistic \( \mathcal{H}_{\text{seg}} \), we fit using \( \mathcal{H}_{\text{hom}} \) (see Fig. 5). This shows that the homogeneous model does a poor job of measuring the brain’s properties: Changes in absorption are only
20% of the true change and for scattering are only 5%. This is due to detected photons spending a large fraction of time in the scalp and skull layers. To take this into account we also compare against local volume-averaged properties \( /H_20849 \) dashed lines in Fig. 5; as expected, the homogeneous model reflects these better than the brain's properties. However, there are two major failures of the homogeneous model: cross talk and nonlinearity. Neither of these failures can be compensated for by any (linear) volume-averaging correction. The absorption and scattering cross talk dominates the fitted \( /H_20849 \) over which \( N_p \) varies from 1.8 \( /H_20850 \) to 3.5 \( /H_20850 \). The error bars show ±1σ about the MAP (best-guess) value for the (marginal) posterior distribution of inferred values, computed by the methods of Appendix A. For comparison, the thin lines show the true values. The fractional model error is \( \epsilon = 0.05 \).

3. Segmented–Segmented Model

We now fit these same \( /H_20849 \) signals with the \( /H_20849 \) model (see Fig. 6). Measurement errors are 2–2.5%
in $\mu_{a,\text{brain}}$ and 5–10% in $\mu_{s,\text{brain}}$ across the complete range of biologically relevant true parameter values. The linearity is excellent, and cross talk causes a 0.5% change in $\mu_{a,\text{brain}}$ and a 5% change in $\mu_{s,\text{brain}}$ across the parameter range. Importantly, although error bars are larger than with $\mathcal{H}_{\text{hom}}$, true values always fall within the error bars. This shows that we believe reliable measurements of the brain’s baseline properties can be made when anatomical information is provided.

Recalling that we are simultaneously fitting for scalp, skull, and brain parameters, we can ask how accurately the scalp and skull have been characterized. At the standard values of Table 1, expected errors are approximately 8% for $\mu_{a,\text{scalp}}$, 3% for $\mu_{s,\text{scalp}}$, 4% for $\mu_{a,\text{skull}}$, and 2% for $\mu_{s,\text{skull}}$.

We believe that in this fitting (nonimaging) example, the total photon number $N_p$ will be more important to determine accuracy than the number of sources and detectors. Only when $N$ is increased, as in an imaging application, or when unknown optode calibration parameters are included, do we expect that an increase in the number of sources and detectors will significantly improve accuracy. Note that generally to optimize the optode location and number, and TPSF parametrization, it would be important to know which components $m$ of the signal $y$ are most important to determine error-bar size for $\mu_{a,\text{brain}}$ and $\mu_{s,\text{brain}}$. Within the Gaussian posterior approximation, all this information is contained in the singular value decomposition of $J$ [defined in Eq. (A6)]. We will present these results in future publications.

B. Systematic Deviations

In this subsection we discuss a detail of the inference procedure. (This can be skipped on first reading.)

The reason why there are systematic deviations between MAP and true parameter values in Figs. 4 and 6 is not immediately intuitive. One might suspect that, because exactly the same models are used for simulation as for inference, zero error would result, averaging over the simulated noise. This effect is worth discussing further. In essence the systematic difference comes from the mismatch between the simulated and the inference noise models: $\sigma_{\text{sim}}(f) \neq \sigma(f)$ for large $f$ [see Eqs. (7) and (6)]. If the inference noise model is correct (i.e., reflects the population from which noisy signals are sampled), Bayesian inference provides unbiased estimators\(^{52}\) (in this case, $x_{\text{MAP}}$ values). We have checked this: If $\sigma_{\text{sim}}(f) = \sigma(f)$ for all $f$, then the deviations change from systematic to random. However, model error is not random; we prefer to investigate its effect in particular cases of realistic model error (see Subsection 4.E).

Mathematically, the systematic deviation can be seen to arise from the weak $x$ dependence of $\sigma(f(x))$ [giving $\sigma'$ terms in Eq. (A2)]. It would be misleading to attempt to correct this deviation as this would be tantamount to benefiting from more information about the system than we have formalized in the noise model of Eqs. (3) and (6). The deviation is always of a size consistent with the error bars; the correct way to reduce this deviation is to build more accurate forward models whose smaller known model error we can then use for inference.

C. Noise Model Effect on Brain Parameter Error Bars

It is natural to wonder what the effects of the number of detected photons $N_p$ and the fractional model error $\epsilon$ are on the measurement accuracy. This allows the experiment designer to know in advance the detection time needed to reach a certain expected error in brain optical properties. In Fig. 7 we plot contours of expected percentage error in the two brain parameters across the $N_p - \epsilon$ plane. We chose the standard set of optical parameters using $\mathcal{H}_{\text{seg}}$ for inference on a noisy signal from the same segmented model. The results show that, even if we assume a fractional model error as large as $\epsilon = 0.2$, expected errors on brain parameters can be 5% for absorption and 15–20% for reduced scattering.

To generate Fig. 7, it would have been a costly operation to find a solution for $x_{\text{MAP}}$ if we located $x_{\text{MAP}}$ for each point in the plane. Instead we observe that, because $f(x)$ is locally linear, its Jacobean $J$ at $x_{\text{MAP}}$ will be similar to that at $x^{(0)}$, when $x_{\text{MAP}}$ is close to $x^{(0)}$. [In our case, it becomes a bad approximation.
only when marginal expected errors are greater than roughly 20%, when nonlinearity of \( f(x) \) becomes relevant. Therefore we can use \( J \) measured once at \( x^{(0)} \) to approximate \( \Sigma_{MAP} \) for any noise model parameters, according to approximation (A5) and Eqs. (A6) and (A7). This procedure makes investigation of the noise model a rapid process.

D. Visualization of Full Posterior Distribution
In Subsection 4.A, for inference with \( H_{seg} \), the error bars (marginal expected errors) in the six parameters were of the same order of magnitude, 2–10%. However, the hyperellipsoid defining the full posterior is actually narrow in some directions; these directions are not aligned with the parameter axes. The ratio of the smallest to largest eigenvalue of \( \Sigma_{MAP} \) is 3 \times 10^3, implying that the shortest principal axis is only approximately 2% of the longest. The distribution is in fact pancakelike. This phenomenon of both well-constrained and poorly constrained parameter directions is a feature of ill-posed inverse problems.

Combined with the nonlinear nature of \( f(x) \), this gives us some motivation to be suspicious of a Gaussian approximation to the posterior. Figure 8 shows that, even when our posterior is much wider (5% in \( \mu_{s,brain} \) and 14% in \( \mu_{s,brain} \)), the Gaussian approximations to the marginal distributions are adequate and would give adequate confidence intervals on each \( x_s \). However, the non-Gaussian nature has become relevant in the tails of the distribution [e.g., at large \( \mu_{s,brain} \), Fig. 8(i)]. We generated the samples from the true posterior by MCMC using the Metropolis method with the stepping distribution chosen to be uniform within a hyperellipsoid of shape given by the Hessian matrix [approximation (A5)]. By optimizing the hyperellipsoid size, we could extract one independent sample from the Markov chain roughly every 40 forward model evaluations. The total cloud took 20 h of CPU time to generate. Faster MCMC methods exist.

Note that in Fig. 8 the conditional distributions (i.e., slices through the posterior; conditional distributions are much easier to generate than true marginal distributions) do a poor job of telling us the width of the marginal distributions. This results from the pancakelike nature of the PDF.

E. Robustness to Forward Model Error
If we run our forward model at a higher lattice resolution, we can generate simulated signals \( y \) that are more accurate, giving the true physics and the tissue segmentation model. In this way we can see how the inference procedure (based on a lower lattice resolution) handles realistic model error, which is highly correlated. In other words, we avoid committing the inverse crime of using identical forward and inverse models, of which we were guilty of in Subsection 4.A.

In Fig. 9(a) we show that a change from a 2-mm to a 1-mm lattice voxel size in the forward model causes changes of roughly 20%. Most are smaller, and some are much larger, approaching 50% at early times. This latter early-time error is due to the non-zero depth below the surface at which the optode couples to the fluence gradient (see Appendix B). The smaller late-time error is due to the voxelated (rough) surface representation local to each optode.

We perform inference using the usual 2-mm lattice model \( H_{seg} \) and the choice of \( \epsilon = 0.2 \) in the inference noise model, motivated by the 20% observed model error. We increase the collection time to yield roughly 1.2 \times 10^7 photons. We find [Fig. 9(b)] that the variance of the resulting normalized residuals \( \beta^{} m \) [see Eq. (A3)] is close to 1, indicating a rough match of the noise model to true forward model errors.

Figure 10 shows the results of sweeping the true brain optical parameters. The accuracy of measurement of \( \mu_{s,brain} \) is approximately 4% and for \( \mu_{s,brain} \) it is 10–20%. The linearity is good, and maximum cross talk is 6% (only significantly affecting \( \mu_{s,brain} \)). The systematic errors are certainly larger than those achieved in the more artificial situation shown in Fig. 6; however, the error bar still does a good job of indicating the size of this error. Therefore model error is being handled in a robust fashion.

Clearly, incorporating the fact that model errors...
be made using a small time-resolved DOT apparatus with high-resolution 3-D anatomical information from MR imaging. We use an automatic MR segmentation into the basic tissue types (scalp, skull, CSF, and brain) and fit for \( \mu_a \) and \( \mu_s' \) of scalp, skull, and brain (holding the CSF fixed), assuming each tissue is optically homogeneous. We perform simultaneous nonlinear model-based fitting (inference) of the six optical parameters and demonstrate the superiority of this approach over a homogeneous head model in the biologically relevant parameter ranges 0.005 mm\(^{-1}\) < \( \mu_a \) < 0.025 mm\(^{-1}\) and 0.5 mm\(^{-1}\) < \( \mu_s' \) < 2.0 mm\(^{-1}\). We emphasize that even the homogeneous head model is more realistic than the commonly used homogeneous semi-infinite slab model. For our research we use numerically simulated noisy measured signals. Our finite-difference forward model can simulate the time-domain diffusion approximation in arbitrary 3-D head geometries; we use approximately \( 3 \times 10^6 \) nodes. We believe that this approximation is adequate given the convoluted CSF geometry, although this an important area of active research for us and others in the field. Fitting takes approximately 10 min on a standard 1-GHz CPU.

We employ a realistic but novel Gaussian noise model incorporating both shot noise, parametrized by the total detected photons \( N_p \), and model error (including calibration) parametrized by a fraction \( \epsilon \). In the Bayesian inference framework, with a flat prior, we find the baseline measurement accuracy (error bars) by examining the marginal width of the posterior distribution for each parameter. We note that all previous demonstrations of Bayesian DOT have either been in two dimensions or simple cuboid geometries and have not considered more than the single best-fit (MAP) solution. We find that \( 2 \times 10^6 \) detected photons yield a 2.5% error bar in \( \mu_s, \) brain and 5–10% in \( \mu_s', \) brain, assuming model errors of 5%. The cross talk between surface layers and the cortex, and between \( \mu_a \) and \( \mu_s' \), present with the homogeneous model is eliminated.

By using a finer computational lattice, we tested a realistic forward model error and found that, even with a 20% model error, the error bars can still be adequate: 4% in \( \mu_a, \) brain and 10–20% in \( \mu_s', \) brain for \( N_p \approx 10^7 \). (All \( N_p \) values could be reduced experimentally by use of per-detector variable attenuation.) Robustness is demonstrated by the fact that error bars always reflect the size of the true deviations. We have also demonstrated the power of MCMC for posterior sampling when the Gaussian MAP approximation is no longer good.

The Bayesian framework allows, without fuss, use of improved noise models. We believe it will be important to encode into such models both measurement properties of the DOT apparatus and physical and numerical human head forward model errors. Noise models should also provide robustness to measurement outliers by replacing the Gaussian with a heavier-tailed distribution. In future studies we plan to include unknown optode amplitude calibra-

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**Fig. 9.** (a) Approximate error of the 2-mm lattice forward model signal expectation, expressed as a ratio against its (more accurate) 1-mm lattice equivalent. The standard set of optical properties is used for the segmented head model. (b) The normalized residual \( \beta_n \), which results when we compare the 1-mm lattice signal with the 2-mm lattice signal using noise model parameters \( y_p = 10^{-4} \) and \( \epsilon = 0.2 \).

**Fig. 10.** Inference by use of the 2-mm lattice forward model \( \Psi_{seg} \) on simulated noisy signals generated from a 1-mm lattice forward model. The detection time was larger than in Fig. 6, with \( N_p \) spanning 1.18 \( \times 10^7 \) to 1.35 \( \times 10^7 \) over the range of \( \mu_a \) and \( \mu_s' \). The fractional model error of \( \epsilon = 0.2 \) was chosen to reflect our knowledge of the 2-mm lattice model errors.
tion parameters, which can then be marginalized over naturally within the Bayesian framework. (We note that Oh et al. have recently simulated Bayesian optode calibration in a 3-D cubical geometry, at least in terms of a single MAP solution, with success.) By increasing the number of parameters from 6 to 10\(^2\) or more, our Bayesian approach could give error bars and correlations of voxel parameters in a true imaging (tomography) context, something we intend to address in future research. In general the value of the Bayesian paradigm in neuroimaging lies with its statistical roots in what is becoming an increasingly statistical practice. On a lower level, information from other modalities can optimally be included as a prior. On a higher level, the full posterior PDF, containing all error correlations, could be fed to dynamical models of neural activation.

Our study provides realistic expectations for achievable baseline accuracy in human hemodynamic parameters. An experimental implementation could have rapid clinical benefit in the stroke and neonatal fields. Our research also expands the possibility of simultaneous DOT and MR for functional neuroimaging: Quantitative optical imaging of hemodynamic changes will require accurate baseline properties, which can best be achieved through the type of anatomical modeling presented here.

Appendix A: Finding the Gaussian Approximation to the Posterior

Maximizing relation (4) is equivalent to minimizing \(L(y; x)\) over \(x\) given the bounds. We rescale the components of \(x\) to have the same typical size by multiplying absorption coefficients by a constant \(C = 10^3\), given, for example, in the fully segmented case \(x = \{C_{\mu_a,\text{scalp}}, C_{\mu_a,\text{skull}}, C_{\mu_a,\text{brain}}, C_{\mu_b,\text{brain}}\}\). This elementary preconditioning enhances the performance of the inference methods presented below.

Because of the nature of the numerical solution of the forward model (Appendix B), the dependence of \(L\) on \(x\) is not completely smooth or differentiable. This jitter in \(L\), although estimated to be on a scale of less than \(10^{-3}\), means that care has to be taken in the choice of an optimization algorithm. We found Newton’s method\(^72\) most successful, the \(i\)th iteration step being

\[
x_{i+1} = x_i - H^{-1}(x_i) \cdot \nabla L(x_i),
\]

where the exact gradient of \(L\) has components

\[
[\nabla L(x)]_n = \sum_{m=1}^{M} \frac{J_{mn}(x)}{\sigma_m} [\beta_m + (1 - \beta_m^2)\sigma_m^2],
\]

which follows from Eq. (3). Here the normalized residual is

\[
\beta_m = \frac{f_m(x) - y_m}{\sigma_m},
\]

and the Jacobian (Frechet) derivative of the forward model is

\[
J_{mn} = \frac{\partial f_m}{\partial x_n}.
\]

The symbol \(\sigma_m\) is an abbreviation for \(d\sigma / df_m|_{x_n}\), which in our case we can find in closed form by differentiating Eq. (6). All quantities are evaluated at \(x\). Because the number of unknowns \(N\) is small, we evaluate \(J\) using crude finite differencing along the axes in \(x\) space:

\[
J_{mn}(x) = \frac{1}{\delta x} [f_m(x + \delta x e_n) - f_m(x)],
\]

where \(e_n\) is the \(n\)th unit vector, requiring \(N + 1\) forward evaluations. With adjoint differentiation it would be possible to obtain \(J\) with an effort roughly equal to one forward evaluation\(^40,41,57\); this would be worthwhile only if \(N\) were larger.

It is simple and efficient to use an approximate Hessian matrix,

\[
H \approx H_{\text{approx}} = \tilde{J}^T \tilde{J},
\]

where

\[
\tilde{J}_{mn} = \frac{\partial^2 f_m}{\partial x_n \partial x_l} = \tilde{J}_{mn} \frac{1}{\sigma_m}(1 - \beta_m \sigma_m'),
\]

is the Jacobean of the normalized residual. This requires no extra function evaluations to be performed. The stopping criterion for locating \(x_{\text{MAP}}\) is \(|x_{i+1} - x_i| < \epsilon\) where \(\epsilon\) is of the order of \(10^{-3}\). The initial value \(x_1\) is chosen randomly in the optical parameter range of interest and has no effect on the \(x_{\text{MAP}}\) found. (Occasionally if \(x_{\text{MAP}}\) is very far from \(x_1\), then an initial rough Nelder–Mead simplex optimization\(^72\) is required.) Typically 3–8–newton iterations are required. Given that a 2-mm lattice evaluation of \(f(x)\) takes approximately 16 s, this means 5–15 min are required to find \(x_{\text{MAP}}\) and \(\Sigma_{\text{MAP}}\).

Because the derivatives of log terms from Eq. (3) are small, the above form of the Hessian usually agrees to within a few percent with a numerically estimated Hessian found by means of finite differencing \(N(N + 1)/2\) samples of \(L\) in \(x\) space. We have experimented with procedures for this estimation, but the combination of jitter on \(L\), the fact that \(L\) is orders of magnitude more sensitive in some directions than others (i.e., the Hessian is close to singular), and the nonlinearity of \(f(x)\) and hence \(L(x)\) causes a tendency for large errors and nonpositive definiteness. Nothing as reliable as the above (guaranteed positive definite) approximate Hessian form has been found. Therefore our multivariate Gaussian covariance matrix estimate is

\[
\Sigma_{\text{MAP}} = (H_{\text{approx}})^{-1}.
\]

To calculate confidence intervals on single parameters, and the lower-dimensional marginal Gaussian distributions shown in Figs. 8(a)—8(c), we need the recipe for marginalizing a multivariate Gaussian onto a subspace. We split \(x\) into subspaces \(a\) and \(b\). By reordering \(x_j\), without loss of generality, this can be written as \(x^T = [a^T, b^T]\). Any covariance \(\Sigma\) in the \(x\) space can then be written in block form:

\[
\Sigma = \begin{bmatrix}
\Sigma_{aa} & \Sigma_{ab} \\
\Sigma_{ba} & \Sigma_{bb}
\end{bmatrix}.
\]
By analytically integrating over \( b \), the inverse covariance of the marginal distribution in subspace \( a \) can be shown to be \(^{23}\)

\[
\Sigma_{(a)}^{-1} = \Sigma_{aa}^{-1} - \Sigma_{ab} \Sigma_{bb}^{-1} \Sigma_{ba}^T.
\]  

(A9)

In the case where \( a \) has a single dimension \( a = x_n \), then \( \Sigma_{(a)} = \sigma_{x_n}^{-1} \) is a scalar giving the marginal standard deviation of parameter \( x_n \).

**Appendix B: Finite-Difference Method for the Diffusion Equation**

Here we provide details of the method used to approximate the time evolution of the 3-D parabolic of Eq. (5) with constant \( \nu(r) = c \). There are many issues, most of which we discuss only cursorily. Because \( q(r, t) \) is nonzero only at \( t = 0 \), this is an initial value problem, and we use a FDTD method with a regular cubical lattice of nodes with spacing \( \Delta x \) and a time step \( \Delta t \). We chose this over finite-element methods for simplicity and the fact that our segmentation map is also based on a cuboid lattice. We chose a node-based representation of fluence \( \phi \) and discretized the spatial derivative at node location \( r_{i,j,k} \) in the standard fashion\(^{72,74,75}\):

\[
\frac{\partial}{\partial x}\left( \kappa \frac{\partial \phi}{\partial x} \right)_{r_{i,j,k}} = \kappa_{i,j,k} \left( \phi_{i+1,j,k} - \phi_{i,j,k} \right) - \kappa_{i-1,j,k} \left( \phi_{i-1,j,k} - \phi_{i,j,k} \right) \Delta x^2,
\]

(B1)

with equivalent expressions in the \( y \) and \( z \) directions, where \( i, j, k \) are integer node labels in \( x, y, z \) axes, respectively. This is second-order accurate in \( \Delta x \). The material property \( \kappa \) is voxel based. We locally average four voxels to give edge-based values \( \kappa_{i\pm1/2,j,k} \).

The initial fluence \( q(r, 0) \) is discontinuous, comprising a delta function (or convolved delta function) near the source; we found that Crank–Nicolson-type \( O(\Delta t^2) \) methods do not handle the nonsmooth fluence well because of the slow decay of nonphysical oscillatory modes excited by the discontinuity. We note that these methods (specifically the alternating-direction implicit method) are commonly used\(^{15,40,41,57}\) for simulation of Eq. (5) without mention of this issue. Instead we use the explicit Euler \( O(\Delta t) \) method, which is less efficient and requires \( \Delta t < \Delta x^2/(6\kappa c) \) at every point in the lattice for stability.\(^{75}\) Evolution is performed by repeated sparse matrix multiplication. Our computational effort is proportional to the number of nodes times the number of time steps: This scales like \( 1/(\Delta x^3 \Delta t) \), which is proportional to \( 1/(\Delta x^3 \mu_{s,min}) \) where \( \mu_{s,min} \) is the smallest value of \( \mu_s \) in the system. Changing \( \Delta x \) from 2 to 1 mm therefore increases the effort by a factor of 32. Implicit methods would be more efficient; we are developing an optimal way to combine explicit and Douglas–Gunn\(^{75}\) evolution to handle the discontinuous initial condition.

We emulated Dirichlet boundary conditions by removing degrees of freedom \( \phi_{i,j,k} \) for nodes on or outside the tissue–air boundary. (The issue of FDTD stability with the more correct Robin boundary conditions is an area for research; we found resulting differences to be slight in our simulations for reasons given in Subsection 3.C.) We simulate only a fraction of the human head volume, corresponding to approximately \( 3 \times 10^4 \) nodes for \( \Delta x = 2 \text{ mm} \). Detector signal relative changes were less than 1% compared with the full head simulation of approximately \( 6 \times 10^5 \) nodes.

To inject and detect fluence signals, we developed lattice versions of standard optode models that couple to the fluence normal gradient \( \nabla \phi \) at the tissue–air boundary.\(^{15}\) To reduce dependence on the detailed local voxel representation of the head surface required that each optode be coupled to the fluence derivative in the beam direction, averaged over a beam of 2-mm radius at the rather large fixed depth of 1.5 voxels below the local surface along the beam direction. This large depth is responsible for the large early-time errors in Fig. 9, but is necessary to maximize immunity to voxelated surface roughness. The source optodes give \( q(r, 0) \); the time-dependent detector signals are then integrated over the time gates to give the components of the signal expectation vector \( f(x) \). Note that this gradient-based source model is equivalent to more usual point-source models, but is more immune to voxelated surface roughness. Exploration of other optode models is an area for future research.

The procedure was validated against known analytic semi-infinite slab solutions (<5% errors beyond 200 ps) and against a Monte Carlo calculation of a heterogeneous cuboid containing an absorbing and scattering inclusion whose nearest approach to the surface was as close as 6 mm (~20% errors). We reserve validation against Monte Carlo in the full head model for a future publication.

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**References and Notes**


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69. Note that for us this acronym does not imply association with hyperbolic equations. We are evolving a parabolic equation.


