

3D OPTO-ACOUSTIC IMAGE RECONSTRUCTION AND MOTION TRACKING USING CONVEX OPTIMIZATION ALGORITHMS

by

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ABSTRACT

This work involves developing techniques for improved opto-acoustic imaging (OA), with the goal of enabling enhanced visualization of vascular structures in biological tissue. This has potential application for diagnosis and detection of cancer and other diseases where blood vessels have structural and functional differences from healthy tissue.

In OA systems, acoustic waves are generated by absorption of optical energy. Since hemoglobin absorbs more light than other molecules in tissue, images of the tissue's blood distribution can be reconstructed by processing measured acoustic signals. Moreover, the wavelength-specific optical absorption of oxy- and deoxy-hemoglobin permits OA to image the blood's oxygen saturation level. However, OA image quality is limited by the ability to localize acoustic sources in tissue, and by the ability to collect sufficient data to accurately reconstruct tissue properties.

To improve OA image quality, this work investigates using convex mathematical optimization to perform image reconstruction from transducer measurements. The proposed technique iteratively solves an inverse problem by fitting the measured data onto simulated OA signals. To accelerate computational performance, mathematical simplifications for 3D simulation and reconstruction are developed. Using multiple acquisitions to provide 3D volumetric information, a method is developed to determine transducer motion from OA data during image reconstruction. In addition, the ability to visualize blood oxygen saturation is characterized for a clinical OA breast imaging device, and image quality is studied using biologically-relevant tissue phantoms.

Results demonstrate that reconstruction with mathematical optimization can achieve higher contrast-to-background ratio (CBR) and peak-signal-to-noise ratio (PSNR) compared to approaches involving backprojection. In addition, using a separable model for the system's response reduces computational complexity by a factor of n in a 3D volume with n^3 voxels. This potentially enables faster and more accurate image reconstruction in OA systems.

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DEDICATION

This work is dedicated to:

*Liam,
Emily
and
Ella.*

SUMMARY CONTENTS

Preliminaries	ii
Chapter 1 Introduction	1
Chapter 2 Opto-acoustic Imaging of Relative Blood Oxygen Saturation and Total Hemoglobin for Breast Cancer Diagnosis	13
Chapter 3 Fast Three-dimensional Opto-acoustic Simulation for Linear Array with Rectangular Elements	53
Chapter 4 Opto-acoustic Image Reconstruction and Motion Tracking using Convex Optimization	105
Chapter 5 Image Reconstruction Combined with Interference Removal using a Mixed-Domain Proximal Operator	155
Chapter 6 Discussion, Conclusions and Future Work	167
Bibliography	175

CONTENTS

Preliminaries	ii
Author's Declaration	ii
Abstract	iii
Acknowledgments	iv
Dedication	v
Contents	vi
List of Tables	x
List of Figures	xi
 Chapter 1 Introduction	 1
1.1 Specific Aims	3
1.2 Hypothesis	4
1.3 Outline	4
1.4 Significance and Contributions	5
References	7
 Chapter 2 Opto-acoustic Imaging of Relative Blood Oxygen Saturation and Total Hemoglobin for Breast Cancer Diagnosis	 13
Abstract	13
2.1 Introduction	14
2.2 Theoretical Background	17
2.3 Methods	18
2.3.1 Biologically relevant phantoms	18
2.3.2 OA/US color maps	21
2.3.3 Sensitivity to differences in oxygen saturation	25
2.3.4 Penetration depth	25
2.3.5 Image analysis	26
2.4 Results	27
2.4.1 Display of vessels in biologically relevant phantom	27
2.4.2 Sensitivity to differences in oxygen saturation	27
2.4.3 Varying of vessel depth and blood hematocrit level	31
2.4.4 Penetration depth	32
2.5 Discussion	32
2.5.1 Characterization of relative s_{O_2} and c_{tHb} with dual-path flow system	32
2.5.2 Differences between phantoms and breast tissue	34
2.5.3 Visualizing relative s_{O_2} and c_{tHb} with statistical color mapping	36
2.5.4 Application of relative s_{O_2} and c_{tHb} for OA/US clinical breast diagnosis	37
2.5.5 Other OA visualization approaches for clinical breast imaging	38
2.5.6 Relationship of statistical mapping with quantitative imaging approaches	38
2.6 Conclusion	39
2.A Appendix	40
2.A.1 Optical absorption of biological tissue	40
2.A.2 Computation of c_{HbO_2} and c_{HbR}	40

Acknowledgment	41
2.S Supplemental Material	42
Statement of Publication	45
Author Contributions	45
References	46
 Chapter 3 Fast Three-dimensional Opto-acoustic Simulation for Linear Array with Rectangular Elements	 53
Abstract	53
3.1 Introduction	54
3.1.1 Outline	54
3.1.2 Significance	55
3.1.3 Relation to other work	55
3.2 Opto-acoustic Simulation Model	57
3.2.1 List of symbols and equations	58
3.2.2 Notation and preliminaries	59
3.2.3 Coordinate frames of linear array	61
3.2.4 Opto-acoustic signals	65
3.3 Separable Cascade	75
3.3.1 Separability of the system response for acoustic pressure	75
3.3.2 Separability with transducer aperture function	77
3.3.3 Separability with obliquity factor	77
3.3.4 Far-field approximation to improve performance	78
3.4 Results and Implementation	81
3.5 Discussion	83
3.6 Conclusion	88
3.A Appendix	89
3.A.1 Proof of Proposition 3.1	89
3.A.2 Proof of Proposition 3.2	92
3.A.3 Proof of Proposition 3.3	93
3.A.4 Proof of Proposition 3.4	95
Acknowledgement	99
Statement of Publication	99
References	100
 Chapter 4 Opto-acoustic Image Reconstruction and Motion Tracking using Convex Optimization	 105
Abstract	105
4.1 Introduction	108
4.2 Background	109
4.2.1 Opto-acoustic signals	109
4.2.2 Image reconstruction using mathematical optimization	110
4.3 System Model	111
4.3.1 Frames collected by linear array	111
4.3.2 Forward model	112
4.3.3 Separable operator for linear array	115
4.4 Image Reconstruction and Motion Tracking	117
4.4.1 Image Reconstruction	117

4.4.2	Two-stage iterative 3D opto-acoustic image reconstruction	118
4.4.3	Image Reconstruction combined with motion tracking	120
4.4.4	Efficient implementation of reconstruction and tracking	121
4.5	Results and Implementation	123
4.5.1	3D reconstruction of digital phantom	123
4.5.2	Reconstruction and motion tracking using digital phantom	124
4.5.3	Reconstruction from clinical data	125
4.5.4	Reconstruction using biologically-equivalent phantom	126
4.5.5	Varying of frame count and transducer geometry	128
4.6	Discussion	128
4.7	Conclusion	128
4.A	Appendix	129
4.S	Supplemental Material	131
4.S.1	Convergence	131
4.S.2	Reconstruction using biologically-equivalent phantom	134
4.S.3	Reconstruction of digital phantom	140
	Acknowledgement	148
	References	148
Chapter 5	Image Reconstruction Combined with Interference Removal using a Mixed-Domain Proximal Operator	155
	Abstract	155
5.1	Introduction	156
5.2	Problem Formulation	157
5.3	Accelerated Proximal Gradient	158
5.4	Reformulated Problem	159
5.5	Implementation	161
5.6	Results	162
5.7	Conclusion	163
	Acknowledgement	164
	Statement of Publication	164
	References	164
Chapter 6	Discussion, Conclusions and Future Work	167
	Discussion, Conclusions and Future Work	167
	References	171
Bibliography		175

LIST OF TABLES

Chapter 2	13
2.1 Optical and acoustical properties of breast tissue at 757nm and 1064nm	20
2.2 Measured optical and acoustical properties of PVCP based phantom	20
2.3 List of collected datasets	26
2.4 Summary of results for RCS.	30
2.S.1 Accuracy assumptions for sensor readings	42
 Chapter 3	 53
3.1 Computation time for simulating 3D volumes	84
3.2 Computational complexity of simulation models.	87
3.3 Symbol names for complexity analysis	87
 Chapter 4	 105
4.1 List of symbols	106
4.S.1 PSNR of 3D reconstructed volumes	147

LIST OF FIGURES

Chapter 2	13
2.1 Opto-acoustic imaging technology for breast cancer diagnosis	14
2.2 Relative OA/US images of malignant lesion.	15
2.3 PVCP based opto-acoustic phantom	19
2.4 Apparatus for s_{O_2} measurement	20
2.5 Statistical Color Mapping	22
2.6 Color palette for OA Relative and OA Total	23
2.7 Oxygenated and de-oxygenated vessels in PVCP phantom displayed with six Imagio [®] image maps.	24
2.8 Characterization of RGB image colorization as oxygen saturation is varied in biologically relevant phantom	28
2.9 Images of PVCP phantom in OA Total and OA Combined mode	29
2.10 Ability to distinguish vessels in biologically relevant phantom	30
2.11 Image colorization vs. s_{O_2} difference	33
2.12 OA Combined and OA Total maps as depth is varied.	34
2.13 Penetration depth results	35
2.S.1 Measurement accuracy of hemoglobin dissociation curve.	44
2.S.2 Measurement accuracy of oxygen saturation	44
Chapter 3	53
3.1 Geometry of an opto-acoustic probe in rotated and translated coordinate system . . .	63
3.2 Cross section of a typical optical energy distribution	74
3.3 Cascaded separable operators for linear array	76
3.4 Spatial impulse responses in the $z = 0$ plane	80
3.5 3D volume consisting of several spherical opto-acoustic sources of equal intensity . .	82
3.6 Simulated time-domain signals generated by opto-acoustic sources	83
3.7 Signals from point source detected by transducer (separable approach).	85
3.8 Signals from point source detected by transducer (approximation)	85
3.9 Simulated data for 0mm and 4mm width transducer	86
3.10 3D volume with spherical absorbers	87
Chapter 4	105
4.1 Multi-wavelength frame acquisition	113
4.2 Separable acoustic response matrix	116
4.3 Jacobian matrices for six frames of digital phantom	121
4.4 digital phantom consisting of two chromophores	124
4.5 Volume rendering of 3D reconstruction	125
4.6 3D reconstruction solved with elevational probe motion	126
4.7 Reconstructed images of a benign breast lesion	127
4.8 Reconstructed 3D volume of benign lesion.	127

LIST OF FIGURES

4.S.1	Cross-sections of reconstructed 3D volumes	131
4.S.2	Normalized error of $\mathbf{p}^{(k)}$ and $\mathbf{x}^{(k)}$ after outer iteration k	132
4.S.3	Position error of y-coordinate by iteration	133
4.S.4	Biologically-equivalent PVCP phantom	134
4.S.5	Cross-sectional slice of biologically equivalent phantom	135
4.S.6	Cross-sectional slice of biologically equivalent phantom	136
4.S.7	PVCP phantom reconstruction as a function of depth	137
4.S.8	Contrast-to-background ratio of vessels	138
4.S.9	3D reconstruction of PVCP phantom with targets	139
4.S.10	3D volume with spherical absorbers	140
4.S.11	Cross-sections of 3D volume	141
4.S.12	Simulated data for 0mm and 4mm width transducer	142
4.S.13	Reconstruction with ideal elements in simulation and model	143
4.S.14	Reconstruction with simulated wide and modeled ideal elements	144
4.S.15	Reconstruction with wide elements in simulation and model	145
4.S.16	Horizontal profile of spherical absorbers	146
4.S.17	Vertical profile of spherical absorbers	147
Chapter 5		155
5.1	Simulated data measurements arranged as a matrix	159
5.2	Results compared in image domain	162
5.3	EMI signal extracted after algorithm completion	163

INTRODUCTION

To diagnose and detect disease, radiologists analyze medical images that internally visualize human tissue and organs. For assessment purposes, it is important that these images provide clinically relevant information that is accurately displayed. Achieving this depends on which imaging modality is used, and on the ability of algorithms to reconstruct images from measurements. Common imaging modalities include MRI (magnetic resonance imaging), CT (computational tomography), PET (positron-emission tomography), ultrasound, and optical methods such as endoscopy, spectroscopy and microscopy [1], [2]. Each modality involves different physical principles, displays different information, and provides different image quality for specific applications. In opto-acoustic imaging (OA), which is a relatively new modality, blood is optically visualized using acoustic waves, permitting deeper visibility than conventional optical approaches. Consequently, OA enables injection-free assessment of diseases that impact vascularity, without using ionizing radiation [3]–[5]. Since image quality influences the ability to interpret OA images, it is important to understand and characterize factors that may lead to improved imaging performance.

This dissertation investigates methods to improve OA image reconstruction. The main interest involves recent clinical studies for breast cancer diagnosis, performed with 2D opto-acoustic imaging systems [3]–[11], where OA is used to visualize blood oxygen saturation (s_{O_2}) and total hemoglobin concentration (c_{tHb}) to determine if lesions are malignant or benign. These studies involved a hand-held probe with a linear ultrasonic transducer array and an integrated light delivery unit, adding OA functionality to conventional ultrasound. Accordingly, this work focuses on the same OA probe geometry and hardware configuration, which has potential for clinical applications. Techniques are studied to improve and characterize OA image quality for data acquired with linear array transducers. In particular, a method is developed that permits a 2D system's data to be used in 3D image reconstruction. By continually acquiring data during free-hand scanning, this work aims to improve image visibility and to augment OA device functionality with multi-frame acquisition. To achieve this: i) a model is developed to simulate signals produced by OA imaging systems; and, ii) convex optimization is used to solve a regularized inverse problem to perform concurrent image reconstruction and motion tracking.

Image reconstruction involves converting measured data (i.e. the detected physical signals recorded from sensors) into a graphical representation (i.e. an image representing the spatial distribution of physical properties of a volume of tissue). In OA, optical absorption generates acoustic signals by causing a sudden thermal expansion within the tissue. To reconstruct a 2D or 3D volume, signals acquired from transducers at multiple surface locations are used to determine a voxel intensity at each image position. This can be computed using analytic formulae that invert

differential wave-equations from boundary measurements [12]–[16], including time-domain [12], [15] and frequency-domain methods [16]–[18]. Image reconstruction can also be performed by solving a regularized inverse-problem using convex optimization [19]–[26].

For proper tissue visualization, reconstructed images must have minimal clutter and distortion. Although several analytic OA inversion formulas exist for performing reconstruction [12], [13], [15], [16], these generally cause distortion unless a reconstructed region of tissue is fully surrounded by detectors to capture all emitted acoustic waves. For tissue surface acquisition, this limits the effectiveness of analytic reconstruction approaches because complete acoustic capturing is not possible. To permit more accurate image reconstruction, convex mathematical optimization uses assumptions about spatial smoothness and image sparsity to fit reconstructed images onto measured data [23]–[27]. This can significantly improve contrast and reduce clutter. However, certain types of interference remain difficult to suppress, especially in 2D imaging systems.

There are several challenges for image reconstruction in 2D OA systems, which occur due to physical and hardware limitations. In these systems, subjects are scanned using a hand-held probe that incorporates an ultrasonic linear-array transducer with an integrated light delivery unit [3], [5], [7], [28]–[35]. The light distribution, which depends on the illumination geometry and optical wavelength, cannot easily be confined to a 2D slice of tissue. This results in interfering acoustic waves produced by out-of-plane optical absorbers. Also, since OA signals have broadband acoustic frequency content, the frequency-dependent spatio-temporal impulse responses of physical transducer elements provide limited interference rejection at high-frequencies, and cannot easily suppress low-frequency out-of-plane signals. Other sources of acoustic interference that create image clutter include secondary waves that are produced and reflected by hardware and tissue during acquisition. Furthermore, electromagnetic interference (EMI) may electronically couple with acquired signals to create temporally-correlated “stripe” artifact. Moreover, light intensity attenuates exponentially, which limits optical penetration and decreases image contrast in deep tissue. Consequently, there is a need for novel approaches to overcome these challenges, and to characterize any improvements.

Several solutions used to improve image quality in conventional ultrasound [1], [36] are not fully applicable to OA. For example, ultrasound hardware adaptations, including directional transducers and acoustic lenses, can have reduced performance in OA at low end acoustic frequencies. As well, in ultrasound, spatial compounding forms images by transmitting multiple ultrasonic pulses at different focus or beam angles. This doesn’t translate directly to OA because OA uses optical pulses. In fact, most OA probes have an optical aperture that remains stationary unless the probe is in motion. In the approach of this dissertation, varying of the light distribution due to probe motion is an advantage that potentially improves image quality. Moreover, motion tracking in the proposed approach differs from freehand motion estimation methods of conventional ultrasound [36]–[45], which involve correlating ultrasonic speckle. In OA, such approaches are less applicable due to differences in the elevational resolution and speckle nature of ultrasound [46].

In imaging devices, image quality is characterized using performance metrics such as contrast-to-background ratio (CBR), penetration depth and peak-signal-to-noise ratio (PSNR) [1]. These measure a system's ability to visualize tissue, and are determined through controlled imaging using calibrated tissue phantoms. In recent clinical OA devices [3]–[11], which visualize relative s_{O_2} and c_{tHb} using statistical color mapping [28], [47], there remains a need to characterize the image quality. In this dissertation, novel methods and performance metrics are developed for characterizing such devices.

Image quality generally improves when unwanted noise and artifacts are reduced. This can be achieved by: i) increasing the signal that is detectable by sensors; ii) by performing reconstruction with additional sensor data; or, iii) by improving algorithms used in reconstruction. Thus, in principle, using convex optimization with additional surface measurements will yield improved OA image quality. In fact, convex optimization guarantees that the best-fitting image that matches the acquired data can be found iteratively using linear algebra, which requires representing the physics of an imaging system as an $M \times N$ matrix (where M is the number of measurements, and N is the number of voxels). With conventional approaches, forming such a matrix (or performing analytic reconstruction) requires prior knowledge of all transducer locations. Consequently, to enable 3D image reconstruction with a hand-held linear-array probe, its motion must be tracked. The need arises for an approach that dynamically incorporates a probe's trajectory into 3D opto-acoustic image reconstruction.

In this dissertation, image reconstruction and motion tracking are combined, which means that variables representing probe motion are solved simultaneously with variables that represent image voxels. Accomplishing this requires investigation and formulation of novel frameworks for standalone 2D and 3D image reconstruction. The resulting improvements to image quality and computational processing speed are studied in the chapters that follow.

1.1 SPECIFIC AIMS

The specific aims of this dissertation are:

1. To develop methods for characterizing the ability of OA devices to visualize blood oxygen saturation and total hemoglobin.
2. To develop methods for rapidly simulating realistic signals from a linear-array OA probe, suitable for solving an inverse-problem.
3. To develop methods for OA image reconstruction using data collected at multiple probe locations.
4. To develop methods for improvement of OA image quality and interference suppression.

Each aim is the focus of one chapter in the body of this work.

1.2 HYPOTHESIS

In contrast to methods for image reconstruction that use analytic formulas involving stationary probe position, the hypothesis of this dissertation is that:

- The ability to visualize tissue using a linear-array OA probe can be improved by performing image reconstruction with convex mathematical optimization and data acquired at multiple probe positions.

1.3 OUTLINE

The body of this dissertation contains four chapters formatted as journal articles. Three of them have been published and one is presently submitted for publication. Each article addresses one specific aim of Section 1.1. Within each article, a literature review and an introduction to basic theory is provided. To avoid redundancy, this is not repeated in Chapter 1.

The chapters are organized as follows:

- **Chapter 1 - Introduction**
- **Chapter 2 - Opto-acoustic Imaging of Relative Blood Oxygen Saturation and Total Hemoglobin for Breast Cancer Diagnosis.** This chapter begins with an introductory overview of OA technology and a review of the literature in the context of clinical breast imaging (Section 2.1). A basic introduction to image formation using multiple optical wavelengths is provided (Section 2.2). The work develops a novel approach to characterize an OA system's ability to visualize relative blood oxygenation and total hemoglobin. This includes development of a biologically relevant phantom, constructed with two independently oxygenated flow paths containing bovine blood, enabling controlled variation of imaging parameters. A linear transducer array is used to acquire phantom datasets, which are reused in Chapter 4 to compare performance. Additional literature review comparing the results to other clinical OA breast imaging techniques is provided in the discussion (Sections 2.5.4-2.5.5). The chapter's appendix (Section 2.A) includes further background about multi-wavelength OA imaging. Lastly, a section describing the chapter's co-author contributions is provided.

This chapter is published in the *Journal of Biomedical Optics* [28].

- **Chapter 3 - Fast Three-dimensional Opto-acoustic Simulation for Linear Array with Rectangular Elements.** This chapter describes theory and mathematics for OA signal generation, beginning with a comprehensive review of relevant literature (Section 3.1). The work develops a novel approach to rapidly simulate OA signals from a dense 3D volume of optical absorbers. The mathematical model used for simulation is formulated as a system response

operator, which is used in Chapter 4 to perform image reconstruction. The model applies to the geometry of a linear array transducer. Rectangular transducer elements, optical fluence distribution, and probe position and orientation are included in the model.

This chapter is published in *IEEE Transactions on Ultrasonics, Ferroelectrics and Frequency Control* [48].

- **Chapter 4 - Opto-acoustic Image Reconstruction and Motion Tracking using Convex Optimization.** Building on the other chapters, this chapter develops a novel approach for 3D image reconstruction using multiple acquisitions from a linear transducer array. In each acquisition, the array records acoustic signals generated by one optical pulse. The chapter begins with a description of the problem and a review of related literature (Section 4.1), followed by background about OA signal generation, image reconstruction and convex mathematical optimization (Section 4.2). By extending the model of Chapter 3, a system response matrix is developed that includes each acquisition's position, orientation and optical wavelength. This is used with mathematical optimization to form 3D images. Moreover, a sequential convex optimization technique is proposed to solve motion tracking during image reconstruction. Results are generated using: i) a digital phantom; ii) the biologically relevant phantom of Chapter 2; and, iii) data collected from a clinical breast imaging study. Using a digital phantom, estimation of elevational probe velocity is demonstrated without using external sensors. The chapter's appendix (Section 4.A) provides relevant background details on using convex optimization algorithms to solve inverse problems.

This chapter is submitted as a journal article to *IEEE Transactions on Computational Imaging*.

- **Chapter 5 - Image Reconstruction Combined with Interference Removal using a Mixed-Domain Proximal Operator.** In this chapter, an approach that combines image reconstruction with electro-magnetic interference removal is proposed. Relevant literature and the problem description are described in Section 5.1. A novel problem formulation is presented in Section 5.2. In Section 5.3, a short introductory background to accelerated proximal gradient algorithms is provided (less detailed than Section 4.A), which is used in Section 5.4 to reformulate the problem so it is more tractable. Results and implementation are in Section 5.5 and Section 5.6.

This chapter is published in *IEEE Signal Processing Letters* [27].

- **Chapter 6 - Discussion, Conclusions and Future Work**

1.4 SIGNIFICANCE AND CONTRIBUTIONS

This work builds on existing approaches for OA imaging, of which clinical feasibility for diagnostic breast imaging has recently been demonstrated [3]–[11]. Methods are developed to improve image quality, which in principle can increase clinical performance, and therefore may broaden

the applicability of OA to visualize various diseases. In addition, methods are developed to characterize OA image quality, helping to relate features detected in OA images with tumor metabolism and function. The limitations of existing methods are studied and new solutions are proposed, specifically addressing requirements for clinical OA imaging devices and hardware. Models and simulations are proposed with special considerations for devices in clinical use, including systems that involve a hand-held linear-array OA probe with an integrated light delivery unit. Lastly, methods, algorithms and their implementations for OA image reconstruction are developed using convex optimization, based on solving an inverse problem to fit measured data onto a simulated model, formulated specifically towards OA physics.

In existing research, several critical aspects of OA have not been previously studied, which constitute the major focus of this dissertation. The first research gap that is examined involves recent clinical OA systems that visualize the relative s_{O_2} and c_{tHb} levels of tissue using statistical color mapping [28], [47]. Methods to characterize an OA system's ability to display this type of information have not been previously developed, and a phantom-based approach to measure image quality for these systems is proposed in Chapter 2. The chapter also presents a new understanding of how relative s_{O_2} and c_{tHb} colorization applies towards breast cancer diagnosis. Related methods in the literature [49], [50] have attempted to characterize a system's ability to display quantitative measurements of s_{O_2} and c_{tHb} ; however, such methods are not applicable for relative colorization, as described in Chapter 2.

The second research gap that is addressed involves the computational performance of modeling realistic OA signals for a linear-array transducer. Solving the inverse problem for 3D reconstruction requires simulating signals from a dense volume of OA absorbers. Existing approaches in the literature do not account for probe location in a global coordinate system, which overlooks computational simplifications that arise when simulating multiple probe locations. The model developed in Chapter 3 proposes that optical illumination moves with the probe's coordinates, corresponding to the illumination geometry of a hand-held OA probe. In addition, mathematical proofs are developed in Chapter 3 to include transducers with realistic rectangular-element aperture and directional sensitivity to acoustic waves, which is more accurate than using simpler omni-directional models of acoustic pressure. In the literature, typical approaches that model realistic transducers involve simulating sources for each element individually [51]–[61], rather than using a single computation for all linear-array elements, as proposed in Chapter 3. Furthermore, separable time-domain computations, as described in Chapter 3, have not previously been applied towards OA. Accordingly, the techniques developed in Chapter 3 significantly accelerate computational performance for OA simulation and reconstruction of a dense 3D volume.

A third research gap addressed in this dissertation is OA image reconstruction using convex optimization, with the goal of improving image quality. In the literature, several methods of OA reconstruction have been implemented using convex optimization or related minimization approaches [23]–[26]. However, these methods have not focused on using the geometry of a hand-held linear-array OA probe. In Chapter 4, the forward simulation model uses data acquired

from multiple probe locations, as well as multiple optical wavelengths. This is unique in that probe position and orientation are represented as parameters that can either be known in advance or solved iteratively. In addition, the forward model incorporates the optical wavelengths for a series of acquisitions into a single system response matrix. This permits existing techniques for solving inverse problems with convex optimization [19]–[22], [62]–[66] to be applied to OA image reconstruction by using the proposed forward model. As the model is novel, this has not been previously attempted. In addition, the motion tracking technique developed in Chapter 4 is novel and further permits improvements to image quality, solving images and motion simultaneously. Chapter 5 continues the theme of improving OA image quality by proposing a new method using convex optimization to suppress electronic interference, formulated with a mathematical derivation to simultaneously solve time-domain and image-domain variables.

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OPTO-ACOUSTIC IMAGING OF RELATIVE BLOOD OXYGEN SATURATION AND TOTAL HEMOGLOBIN FOR BREAST CANCER DIAGNOSIS

2



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ABSTRACT

Opto-acoustic imaging involves using light to produce sound waves for visualizing blood in biological tissue. By using multiple optical wavelengths, diagnostic images of blood oxygen saturation and total hemoglobin are generated using endogenous optical contrast, without injection of any external contrast agent and without using any ionizing radiation. The technology has been used in recent clinical studies for diagnosis of breast cancer to help distinguish benign from malignant lesions, potentially reducing the need for biopsy through improved diagnostic imaging accuracy. To enable this application, techniques for mapping oxygen saturation differences within tissue are necessary. Using biologically-relevant opto-acoustic phantoms, we analyze the ability of an opto-acoustic imaging system to display colorized parametric maps that are generated using a novel statistical mapping approach. To mimic breast tissue, a material with closely matching properties for optical absorption, optical scattering, acoustic attenuation and speed of sound is used. The phantoms include two vessels filled with whole blood at oxygen saturation levels determined using a sensor-based approach. A flow system with gas-mixer and membrane oxygenator adjusts the oxygen saturation of each vessel independently. Datasets are collected with an investigational Imagio[®] breast imaging system. We examine the ability to distinguish vessels as the oxygen saturation level and imaging depth are varied. At depth of 15mm and hematocrit of 42%, a sufficient level of contrast to distinguish between two 1.6mm diameter vessels was measured for an oxygen saturation difference of approximately 4.6%. In addition, an oxygenated vessel was visible at a depth of 48mm using an optical wavelength of 1064nm, and a de-oxygenated vessel was visible to a depth of 42 mm with 757nm. The results provide insight toward using color mapped opto-acoustic images for diagnosing breast cancer.

2.1 INTRODUCTION

Over the past 25 years, a growing community of researchers, clinicians and device manufacturers have been investigating and developing translational opto-acoustic (OA) imaging technologies with the aim of improving clinical care for several diseases [1]–[6]. For breast cancer diagnosis, one promising technique is OA imaging combined with ultrasound (OA/US) [7]–[20]. Combining OA with ultrasound is advantageous because each modality provides information that is complementary to the other. Structural and functional information pertaining to *total hemoglobin concentration* (c_{tHb}) and *blood oxygen saturation* (s_{O_2}) can be visualized with OA, while morphological and anatomical information can be obtained with ultrasound. In conventional ultrasound, which is commonly used to assess and characterize breast masses, there is large overlap between benign and malignant image features, which results in false positive cases that must be confirmed with subsequent biopsy [21]–[23]. However, OA can provide *functional* information about the metabolism of tumors by imaging blood and vascular structure, which may further differentiate benign from malignant masses and potentially lead to improved patient care.

OA involves several physical principles that make it ideally suited for diagnostic breast imaging. Due to the composition of breast tissue, scattered light can penetrate to a depth of several centimeters, which is suitable for clinical applications. Furthermore, using light means that OA safely visualizes the optical contrast of tissue. By selecting specific optical wavelengths, OA can be optimized to endogenously detect certain molecules, which enables visualizing differences in oxygenated and deoxygenated blood. An illustration showing a hand-held OA probe emitting light at two different optical wavelengths is shown in Figure 2.1. The probe measures acoustic

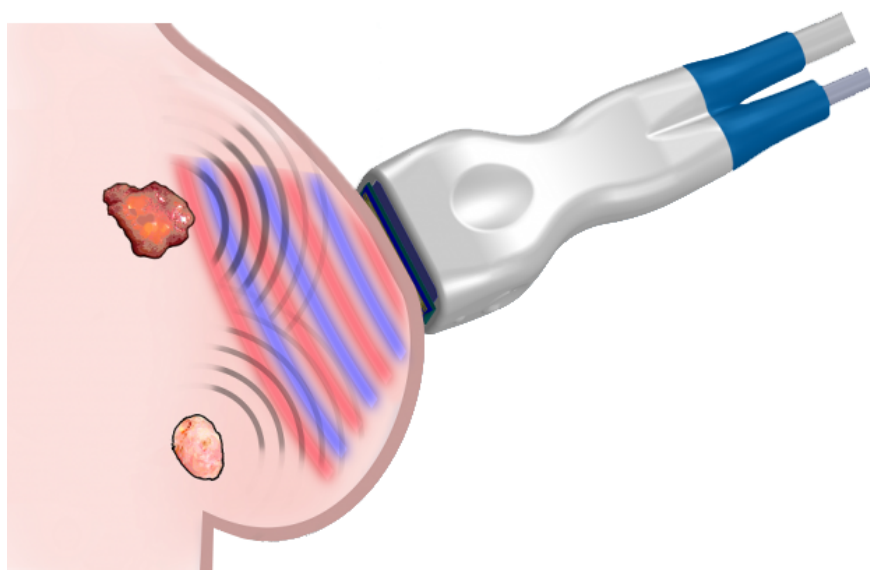


Figure 2.1: Opto-acoustic imaging technology for breast cancer diagnosis. A hand-held OA probe uses light and sound to visualize benign and malignant lesions. Laser pulses at dual optical wavelengths produce a detectable acoustic response in tissue that depends on c_{tHb} and s_{O_2} .

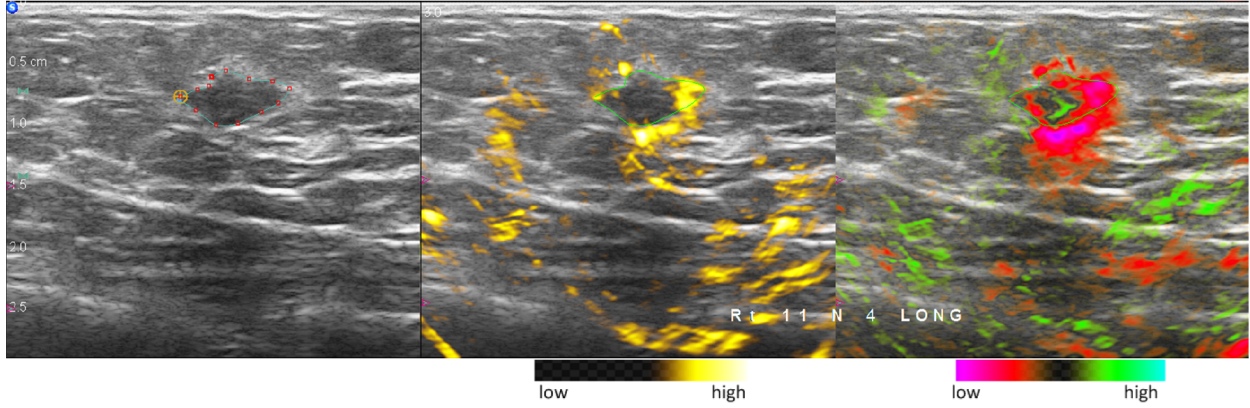


Figure 2.2: Relative OA/US images of malignant lesion. The image maps are Ultrasound (left), OA Total (center), and OA Relative (right). The central nidus of the lesion is segmented with a cyan color outline. Histopathology conducted after excision revealed this grade III invasive ductal carcinoma (GR3-IDC) had extensive internal necrosis. This may account for the lack of internal OA signal within the central nidus, as vessels are not present in the necrotic region. In OA Total, strong signal (yellow) due to hemoglobin is observed in the boundary zone of the lesion. Strong relative de-oxygenation (red) is observed in the boundary zone of the OA Relative map. The image features are consistent with neoangiogenesis and are interpreted here as signs of malignancy.

waves, which are generated by blood and other tissue structures when they are illuminated. From the measured waves, OA images are formed that display the functional composition of tissue. Typically, benign lesions have normal blood vessels and normal oxygen saturation. Malignant lesions are metabolically more active, and tend to have higher vascularity, irregular blood vessels and decreased oxygen saturation [24]–[28]. Since OA directly visualizes c_{tHb} and s_{O_2} , this can potentially give clinicians the ability to perform more accurate diagnosis [7]–[15]. In OA/US, the probe also acquires conventional ultrasound images, which are co-registered and displayed simultaneously with OA.

An immediate goal for OA/US is to potentially allow downgrading mildly suspicious masses to a category where biopsy is not required, without increasing the number of missed cancer cases [9]–[15]. It is estimated that over 1.6 million breast biopsies are performed in the United States each year [22], [23]. A large percentage of these biopsies are negative, which is due to low positive predictive value (PPV) of the imaging modalities presently used for assessment [21], [23]. A possible reduction in the total number of breast biopsies could greatly improve patient care and potentially reduce overall health care costs [23].

Several groups have conducted clinical research studies involving OA, where breast lesions were imaged in human subjects [7]–[16], [29]–[42]. Scanning devices include full-breast 3D imaging systems [29]–[41], as well as real-time 2D hand-held technologies [7]–[18], [42], [43]. To date, the largest clinical effort surrounds the Imagio[®] breast imaging system (Seno Medical Instruments, Inc., San Antonio, TX), a 2D system which has evaluated breast lesions in over 2000 subjects [7]–[16], [19]. The system displays qualitative OA/US maps to visualize areas of strong relative s_{O_2} and c_{tHb} using a *statistical color mapping* technique [44]. The OA/US image maps from a

malignant lesion are shown in Figure 2.2. In this example, the *relative* spatial distributions of c_{tHb} and s_{O_2} indicate presence of hemoglobin and relative deoxygenation in the boundary zone of the lesion. These features are consistent with malignancy and are not apparent from the conventional ultrasound map. In a multi-center Pivotal [7] study, consisting of 2105 subjects from 16 sites, radiologists assessed the presence of specific OA features, similar to those shown in Figure 2.2. OA/US was found to exceed diagnostic specificity of ultrasound by 14.9% [7]. For negative OA/US findings, a maximum pre-test probability of malignancy of 17.8% could potentially be downgraded with OA/US to a post-test probability of 2% [7]. These studies demonstrated that diagnostic assessment of relative OA/US maps may potentially reduce the number of false-positive exams and potentially decrease the total number of performed biopsies.

To assess imaging performance in OA/US, there remains a need for approaches to characterize *relative* image maps, capable of describing how statistical color mapping relates to actual c_{tHb} and s_{O_2} levels. In relative maps, instead of conveying quantitative numerical parameters, which are often difficult to determine, the colorization dynamically adjusts to display high contrast regions from a spatial distribution of values. To characterize this, different levels of relative contrast must be physically reproduced by a phantom that has properties similar to biological tissue. For OA, suitable background materials include gelatin [45], [46], gel-wax [47], and PVCP (polyvinyl chloride plastisol) [48]–[52]. Previously, a phantom comprising channels filled with bovine blood was described for quantitative OA characterization [53], [54]. However, this involved a single flow-path, providing only one s_{O_2} level, which is insufficient for relative characterization. To deal with this limitation, in earlier work, we presented images where two s_{O_2} levels were used for validation purposes [12], but performance characterization was not described.

In this article, an approach for characterizing relative OA/US color maps is presented, which relates RGB image colorization to controlled s_{O_2} and c_{tHb} levels. To quantify performance, we developed a biologically relevant phantom, and a dual-path perfusion flow system, to emulate relative oxygenation differences between two vessels. The two-vessel configuration permits analyzing differences in relative colorization when both vessels are imaged simultaneously. The first objective was to evaluate *relative contrast sensitivity* (RCS), which is defined as the minimum resolvable difference in s_{O_2} between two vessels, when using statistically mapped colorization. The initial results were published in our accompanying proceedings paper [55]. Here, we also measure the impact on RCS, when varying the imaging depth and blood hematocrit level. In addition, we analyze *penetration depth* by simultaneously assessing the contrast-to-background ratio (CBR) of an oxygenated vessel and a deoxygenated vessel. Lastly, we discuss these results in a broader context, where relative s_{O_2} and c_{tHb} maps are used to distinguish benign from malignant breast lesions.

2.2 THEORETICAL BACKGROUND

To provide context for our approach, we describe how OA signal is generated from biological tissue and how this affects image formation. In tissue, blood is the dominant optical absorber of near-infrared light. It contains both oxygenated hemoglobin (HbO_2) and de-oxygenated hemoglobin (HbR), which are molecules that have different wavelength-specific optical absorption. For example, light at 757nm is absorbed more strongly by HbR compared to HbO_2 , but at 1064nm this is reversed.

When molecules absorb light, they heat up, which causes thermal expansion. The *optical absorption coefficient* $\mu_a(\lambda, \mathbf{x})$ of a material determines the amount of light converted to heat. This is a function of optical wavelength λ , as well as position $\mathbf{x} = (x, y, z)$, since molecular composition varies spatially. A material property called the *Grüneisen parameter* $\Gamma(\mathbf{x})$ quantifies how the added heat is converted to pressure*. The *radiant fluence* $\Phi(\lambda, \mathbf{x})$ is the amount of light, at wavelength λ , that reaches position $\mathbf{x}$. Following a rapid heating†, an *initial excess pressure* $p_0(\lambda, \mathbf{x})$ is generated, which is equal to

$$p_0(\lambda, \mathbf{x}) = \mu_a(\lambda, \mathbf{x}) \times \Gamma(\mathbf{x}) \times \Phi(\lambda, \mathbf{x}). \quad (2.1)$$

The generated pressure propagates acoustically, from each position $\mathbf{x}$ to transducers on the tissue surface, delayed according to the speed of sound. The received signal amplitude is proportional to $p_0(\lambda, \mathbf{x})$. Since blood has a much stronger μ_a compared to background tissue, the comparatively strong signal from blood leads to high endogenous image contrast.

In addition to dependence on λ , the optical absorption of blood depends on its s_{O_2} level, which represents the percentage of hemoglobin that is oxygenated [1], [56], [57]. The s_{O_2} can be determined from the *hemoglobin mass concentrations* c_{HbO_2} and c_{HbR} , according to

$$s_{\text{O}_2} = \frac{c_{\text{HbO}_2}}{c_{\text{HbO}_2} + c_{\text{HbR}}}. \quad (2.2a)$$

The total hemoglobin concentration is

$$c_{\text{tHb}} = c_{\text{HbO}_2} + c_{\text{HbR}}. \quad (2.2b)$$

The optical absorption from biological tissue is described in Appendix 2.A.1. By considering only HbO_2 and HbR , this can be written in terms of s_{O_2} and c_{tHb} as

$$\mu_a = c_{\text{tHb}} \times [s_{\text{O}_2} \times \epsilon_{\text{HbO}_2} + (1 - s_{\text{O}_2}) \times \epsilon_{\text{HbR}}], \quad (2.3)$$

which is obtained by substituting (2.2a) and (2.2b) into equation (2.A.1). The *optical extinction coefficients* $\epsilon_{\text{HbO}_2}(\lambda)$ and $\epsilon_{\text{HbR}}(\lambda)$ describe absorption per unit concentration. Equation (2.3) illustrates that μ_a is proportional to c_{tHb} . Since c_{tHb} depends on the *hematocrit level* α_{hct} of blood [55], [58], [59], the OA signal strength is a function of α_{hct} .

* The Grüneisen parameter $\Gamma = \frac{\beta}{\kappa \rho C_V}$ depends on thermal expansion coefficient β , compressibility κ , specific heat capacity at constant volume C_V , and mass density ρ .

† Efficient signal generation occurs when *thermal confinement* (negligible heat diffusion) and *stress confinement* (negligible wave propagation) are achieved during the heating interval.

The OA signal strength is also a function of depth. In equation (2.1), Φ depends on the system illumination geometry, as well as the wavelength-specific optical properties of the medium, including its optical absorption coefficient $\mu_a(\lambda, \mathbf{x})$, *optical scattering coefficient* $\mu_s(\lambda, \mathbf{x})$, and *anisotropy parameter* $g(\lambda, \mathbf{x})$ [59]–[61]. In tissue, $\Phi(\lambda, \mathbf{x})$ can be approximated based on a wide-beam diffusion approximation using an *effective optical attenuation* coefficient $\mu_{\text{eff}}(\lambda)$ [60]. In this case, at depth y and with surface exposure $q_0(\lambda)$, the fluence, at $\mathbf{x} = (x, y, z)$, is

$$\Phi(\lambda, \mathbf{x}) = q_0(\lambda) \times e^{-\mu_{\text{eff}}(\lambda)y}. \quad (2.4)$$

Since $\Phi(\lambda, \mathbf{x})$ influences the received signal, it can impact the OA image quality as well as the penetration depth. Also, in tissue, it is commonly assumed that $\Gamma(\mathbf{x})$ in equation (2.1) does not vary significantly, compared to $\Phi(\lambda, \mathbf{x})$ and $\mu_a(\lambda, \mathbf{x})$, so it can be treated as a constant.

For OA imaging, estimates of s_{O_2} and c_{tHb} are computed. Typically, this involves using data recorded by transducers to reconstruct a map of the initial pressure $p_0(\lambda, \mathbf{x})$ to solve unknown molecular concentrations. For c_{HbO_2} and c_{HbR} , this can be computed as described in Appendix 2.A.2. To compute s_{O_2} and c_{tHb} , the computed c_{HbO_2} and c_{HbR} are substituted into (2.2a) and (2.2b).

Our approach to display relative parametric maps based on s_{O_2} and c_{tHb} , which uses a statistical mapping procedure, is presented in Section 2.3.2. The characterization of these relative maps is described in the next section.

2.3 METHODS

2.3.1 Biologically relevant phantoms

PVCP background material

To characterize the ability to display relative OA/US images, a PVCP based opto-acoustic phantom was constructed to mimic breast tissue, as shown in Figure 2.3. Breast consists of parenchymal and adipose tissue, which have different optical and acoustical properties that are affected by several factors, including age, menopausal state, and the presence of lesions [50], [62], [63]. The biologically relevant ranges for breast tissue properties are shown in Table 2.1. This assumes the range $0.5 - 0.3\text{cm}^{-1}$ for optical absorption of near-infrared light [50]; $1430 - 1520 \text{ m/s}$ for acoustic speed of sound [50]; and $1 - 25 \text{ dB/cm}$ for acoustic attenuation (at broadband frequency range) [50]. The volume fraction of blood $f_{v,\text{blood}}$ is approximately 1.0% for parenchymal breast tissue, and 4-10% for invasive breast cancers [64]. The reduced optical scattering coefficient follows a non-linear fit of $\mu'_s(\lambda) = a\lambda^{-b}$, with $b = 0.99 \pm 0.35$ for breast tissue [59], [65]. Thus, for optical wavelengths of 757nm and 1064nm, we obtain $\mu'_s(757\text{nm}) = 9.4\text{cm}^{-1}$ and $\mu'_s(1064\text{nm}) = 6.8\text{cm}^{-1}$, with variability of around ± 2.5 , using $a = 6700$, which is consistent with other published values.

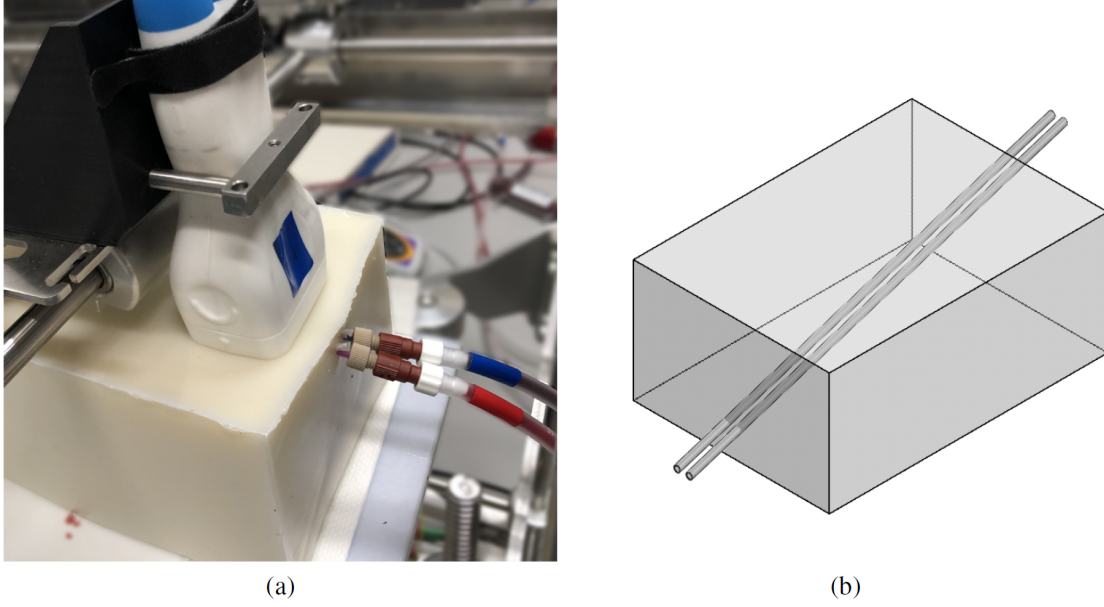


Figure 2.3: PVCP based OA phantom. Two vessels are filled with bovine blood at independently controlled s_{O_2} levels.

In our PVCP phantom, the optical and acoustical properties were tuned, using a similar formulation to Vogt et al. [50], which included TiO_2 and carbon black. The optical absorption coefficient μ_a , anisotropy parameter g , and the reduced scattering coefficient[‡] μ'_s of the phantom were measured using inverse adding and doubling [66] as shown in Table 2.2.

Vessel configuration

Two vessels of inner diameter 1.6mm were embedded in the phantom, as shown in Figure 2.3b. The vessels consisted of Teflon tubing and were sloped at a 17° incline to permit varying of depth during imaging.

Blood preparation

During testing, the vessels were filled with bovine blood (Innovative Research Inc., Catalog No.: IR1-040N), which has optical properties that are similar to human blood [67], [68]. The blood was treated with an anticoagulant (sodium citrate). The hematocrit of the whole blood was analyzed by filling capillary tubes (Fisher, P/N: 22-362-574) with the blood sample and sealing one end with sealing compound (Fisher, P/N: 02-678). Samples were then placed in a micro hematocrit centrifuge for 5 minutes. Using calipers, the length of the red cell volume and the length of total volume were measured. The ratio represents the packed cell volume (PCV) which corresponds to the hematocrit level. For testing that involved using blood at lowered hematocrit levels, the

[‡] The reduced scattering coefficient is related to the scattering coefficient by $\mu'_s = \mu_s(1 - g)$.

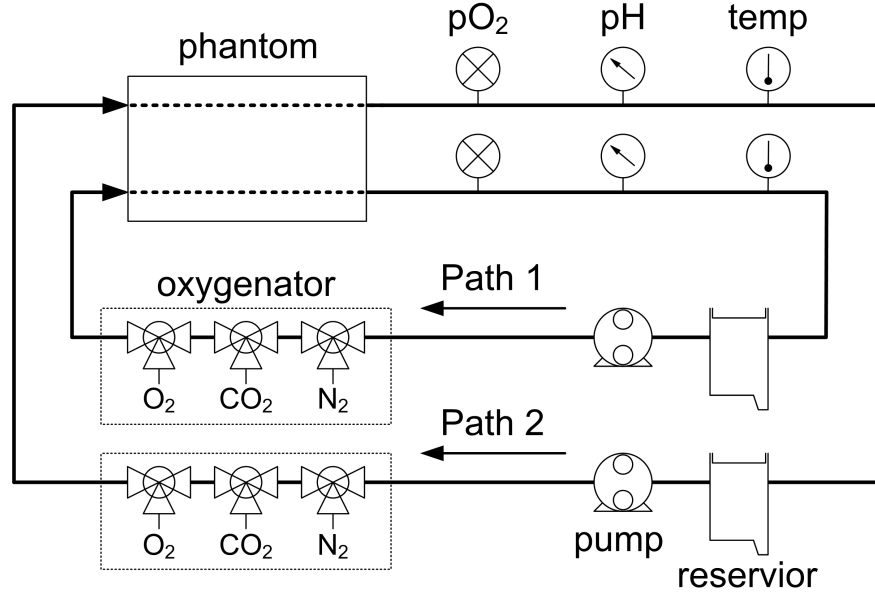


Figure 2.4: Controlled s_{O_2} measurement apparatus. Two independent paths of bovine blood at controlled oxygenation levels are circulated through the phantom with perfusion flow system. A gas-mixer delivers O_2 , CO_2 and N_2 to a membrane oxygenator. Sensor readings for temperature, dissolved oxygen pressure and pH are used to monitor the s_{O_2} level.

whole blood was diluted using sterile PBS (phosphate-buffered saline; MP Biomedicals, Catalog#: 1860454). The hematocrit of the diluted blood was then re-measured using the same procedure described above.

Table 2.1: Optical and acoustical properties of breast tissue at 757nm and 1064nm

Optical Properties	757nm	1064nm
Absorption μ_a (1/cm)	0.05 – 0.3	0.05 – 0.3
Reduced Scattering μ'_s (1/cm)	9.4 ± 2.5	6.8 ± 2.5
Anisotropy g (-)	~ 0.95	~ 0.95
Acoustical Properties		
Speed of sound (m/s)	1430 – 1520	
Attenuation (dB/cm)	1 – 25	

Table 2.2: Measured optical and acoustical properties of PVCP based phantom

Material: PVCP (plastisol)		
Optical Properties	757nm	1064nm
Absorption μ_a (1/cm)	0.089 ± 0.014	0.279 ± 0.055
Reduced Scattering μ'_s (1/cm)	7.90 ± 0.20	6.14 ± 0.07
Anisotropy g (-)	0.80 ± 0.08	0.77 ± 0.01
Acoustical Properties		
Speed of sound (m/s)	1475	
Attenuation (dB/cm)	0.9 – 8.3	

Dual-path perfusion flow system

A dual-path perfusion flow system was used to independently control the s_{O_2} of each vessel. This is schematically illustrated in Figure 2.4. The perfusion flow system was driven by a peristaltic pump (Masterflex, Model: 75728-10) that pulled blood from a reservoir to a membrane oxygenator (Permselect, Model: PDMSXA-2500), to balance the dissolved gas levels of oxygen, nitrogen, and carbon dioxide. The gas supply consisted of a tank of each pure compressed gas. In each path, the tanks were connected to a single gas-mixer (MCQ, Model: GB 100), to control the flow and combine it into a single output connected to an oxygenator. To determine s_{O_2} level, the partial O_2 pressure, pH level, and temperature were monitored using sensors. Dissolved CO_2 influences the pH level of blood. This was initially adjusted to establish a pH level of 7.4 using a pH meter (Denver Instruments, Model: UB-10). The partial O_2 pressure was measured by a pair of dissolved oxygen (DO) meters (Oakton, Model: DO-450), which also record temperature to $\pm 0.1^\circ C$. The meters output DO as a percentage of the calibrated partial pressure of oxygen at atmospheric pressure. As shown in Figure 2.4, in each path, the blood flowed from an oxygenator directly to the phantom and then to a DO meter before returning to the reservoir.

To determine known s_{O_2} levels for blood in both vessels, we established a measurement approach based on DO sensor readings. Oxygen saturation in blood varies according to known *hemoglobin dissociation curves* [69]. These curves model how s_{O_2} changes as a function of partial oxygen pressure, pH level and temperature, and to a lesser extent on partial pressure of CO_2 and DPG (2,3-diphosphoglycerate) concentration. A mathematical relationship to determine oxygen saturation from these variables is described by Dash et al. [69]. A published Matlab function [69] for computing s_{O_2} based on the Dash model was used in the present analysis to relate sensor readings to s_{O_2} values.

An investigation of the measurement accuracy of using hemoglobin dissociation curves was also performed by varying input parameters in the Dash model to compute error-bars for s_{O_2} measurement. It was determined that the highest accuracy occurs near full deoxygenation and full oxygenation. This is due to the lower slope of the oxygen dissociation curves at the extremes. A greater uncertainty was found for mid-level s_{O_2} values. This analysis of measurement accuracy is provided as Supplemental Materials [70].

2.3.2 OA/US color maps

Statistical color mapping

We performed characterization on relative s_{O_2} and c_{tHb} maps of the PVCP phantom that were acquired using an investigational Imagio[®] system. The maps were generated using a statistical color mapping approach, consisting of two steps. First, statistics were analyzed from a reference region of each map to automatically determine color scaling and offset parameters. Next, using

these parameters, a color mapping was applied to display opto-acoustic information from areas of strong signal, relative to background tissue. Figure 2.5 illustrates how statistical mapping applies a color palette to oxygenation levels for several different scaling and offset parameters.

For determining the mapping, the reference region of each map is selected to include average background tissue, so statistical information about the background can be gathered. The choice of the reference region influences the colorization, since different regions have different statistical properties. Commonly, it is set to encompass the entire mid-field tissue region (e.g. 5mm to 30mm depth). However, to analyze certain objects, the reference region can also be set to encompass the upper and lower bounds of a target (or targets) of interest (e.g. the vessels of the phantom), which puts higher weight on the statistics of the targets themselves. Color mapping parameters are obtained by computing a mathematical characteristic applied to s_{O_2} or c_{tHb} intensity values of the reference region. In particular, the average signal level of reference region is used as a color midpoint, to determine the offset parameter. The color scaling parameter is computed based on the standard deviation of the reference region to maximize the contrast level displayed. As a result, for s_{O_2} , this qualitatively highlights regions of significance that have higher or lower levels of oxygen saturation than the reference level. In addition, a transparency mask is generated to permit only regions exceeding a specific colorization level to be displayed.

Figure 2.6 illustrates the RGBA palettes that are used for s_{O_2} and c_{tHb} . Mathematically, a RGBA color palette defines a *color-mapping function* $f_{RGBA} : \mathbb{R} \rightarrow \mathbb{R}^4$, by mapping a real value to three color channels (red, green, and blue) and a transparency channel (alpha).

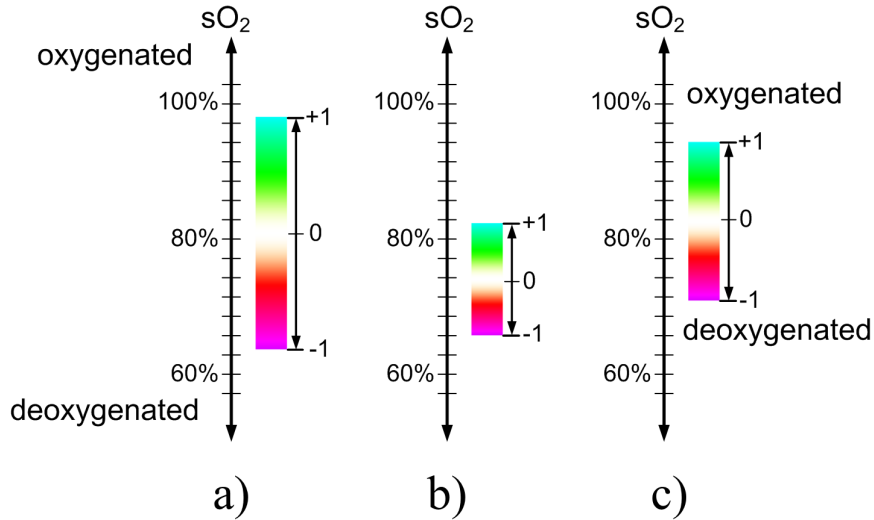


Figure 2.5: Statistical color mapping is used to maximize functional contrast for a region of tissue. The mapping parameters are automatically computed to display areas of high and low s_{O_2} , relative to a background reference level. In a), b) and c), the vertical axis illustrates color mapping corresponding to three images with different statistical properties.

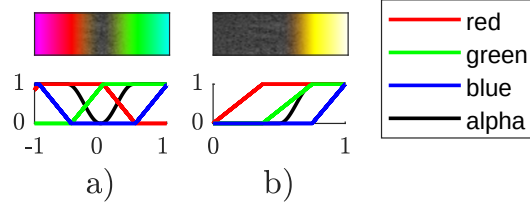


Figure 2.6: Color palette for a) OA Relative and b) OA Total. The function $f_{\text{RGBA}} : \mathbb{R} \rightarrow \mathbb{R}^4$ maps a real value onto 3 color channels and alpha transparency channel.

To perform color mapping, let the estimated values for either $s_{\text{O}_2}(\mathbf{x})$ or $c_{\text{tHb}}(\mathbf{x})$ be represented by a function $f(\mathbf{x})$. The estimated values arise from using equation (2.A.3) with equation (2.2). Since position is represented by $\mathbf{x} = (x, y, z)$, for 2D imaging, we assume $z = 0$. Let $\mathcal{R}$ represent a reference region with N pixels. The mapping function is offset and scaled by the mean μ and standard deviation σ of $f(\mathbf{x})$ in $\mathcal{R}$, where

$$\mu = \frac{1}{N} \sum_{\mathbf{x} \in \mathcal{R}} f(\mathbf{x}), \quad \sigma = \sqrt{\frac{1}{N-1} \sum_{\mathbf{x} \in \mathcal{R}} (f(\mathbf{x}) - \mu)^2}. \quad (2.5)$$

The four-channel color-mapped RGBA image is

$$\begin{bmatrix} v_{\text{R}}(\mathbf{x}) \\ v_{\text{G}}(\mathbf{x}) \\ v_{\text{B}}(\mathbf{x}) \\ v_{\text{A}}(\mathbf{x}) \end{bmatrix} = f_{\text{RGBA}} \left(\text{clip} \left(\frac{f(\mathbf{x}) - \mu}{k_{\text{g}} \sigma} \right) \right), \quad (2.6)$$

where

$$\text{clip}(u) = \begin{cases} k_{\min}, & \text{if } u < k_{\min}, \\ k_{\max}, & \text{if } u \geq k_{\max}, \\ u, & \text{otherwise.} \end{cases}$$

To produce RGB output, the RGBA data of (2.6) is overlaid with a grayscale ultrasound image by blending of the alpha transparency channel. The function $\text{clip}(u)$ is used to ensure the values are between $k_{\min}$ and $k_{\max}$, which represents the domain of f_{RGBA} . Values below $k_{\min}$ or above $k_{\max}$ will be saturated at the maximum or minimum colors of the palette. For the color palette in Figure 2.6a, the values are mapped from the domain -1 to 1; for Figure 2.6b, they are mapped from 0 to 1. The parameter k_{g} represents a gain constant.

Display of OA/US maps

To display opto-acoustic information, Imagio[®] generates six individual image maps, arranged as a six-on-one composite image. A representative image is shown in Figure 2.7. Three of these are colorized image maps that are overlaid with conventional grayscale ultrasound (top left). These colorized maps are called *OA Total* (bottom left), *OA Combined* (top middle), and *OA Relative*

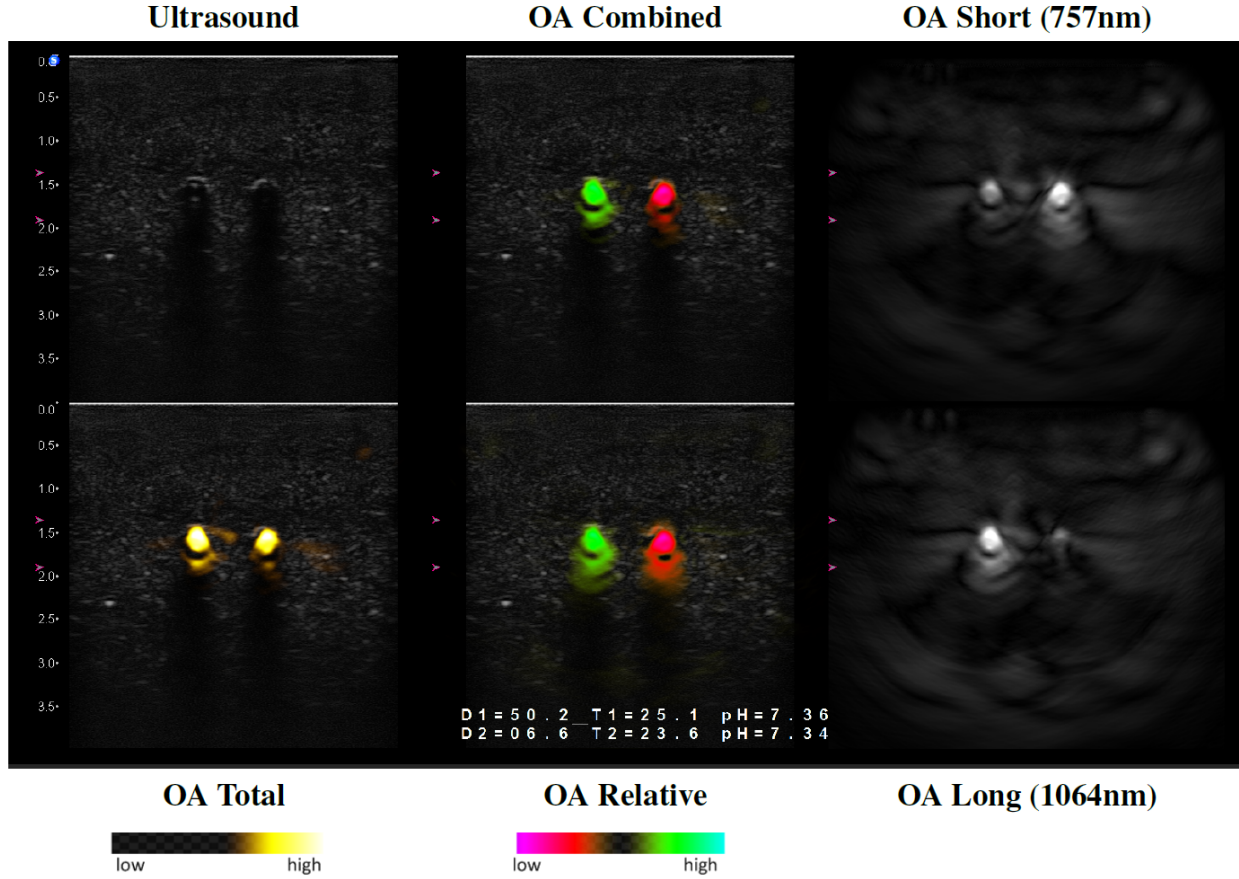


Figure 2.7: Oxygenated and de-oxygenated vessels in PVCP phantom. The circular cross-sections from both vessels are visible in each of the six maps (top row: Ultrasound, OA Combined, and OA Short; bottom row: OA Total, OA Relative and OA Long). The measured s_{O_2} levels are 99% for Vessel 1 (left, green) and 31% for Vessel 2 (right, red). The vessel depth is 15mm, and the field of view (maximum image height) is 40mm.

(bottom middle). Color palettes for s_{O_2} and c_{tHb} are shown in Figure 2.6. The OA Total map is computed based on c_{tHb} . In this map, areas with high relative value appear yellow, and areas with low value are transparent. The OA Relative map is computed based on s_{O_2} . Areas with high relative value appear green, while areas with low value appear red. Areas with mid-range values are transparent. The OA Combined map uses the same RGB values that were computed for OA Relative, but combines the transparency channel of OA Total with the transparency of OA Relative to display signal that is strong in both maps. The OA Total, OA Relative, and OA Combined image maps are generated according to the statistical mapping procedure. The OA Short (top right) and OA Long (bottom right) maps correspond to signal detected at optical wavelengths of 757nm and 1064nm. The 757nm wavelength most strongly detects HbR, whereas the 1064nm wavelength strongly detects signal from HbO₂. Figure 2.7 displays image maps from scanning the biologically-relevant PVCP phantom at controlled s_{O_2} levels. The appearance of vessels in the maps is described with the results of Section 2.4.1.

2.3.3 Sensitivity to differences in oxygen saturation

To determine RCS, the biologically-relevant PVCP based phantom was imaged using an investigational Imagio[®] system. The positioning of the probe relative to the phantom is shown in Figure 2.3. The vessels were oriented perpendicular to the imaging plane. A representative image of the configuration is shown in Figure 2.7. A reference region with a vertical size of 5mm encompassed the vessels, as indicated by markers (magenta arrows).

Several tests were performed, with the procedure repeated for varied imaging depth, oxygenation conditions, and hematocrit levels, according to Table 2.3. In each test, image output in six-on-one format (described in Section 2.3.2) was continually collected while the s_{O_2} levels of both vessels were individually controlled. Since the vessels in the phantom are sloped at an incline, the vessel depth was adjusted for each test by an initial positioning of the probe. A clamp was used to keep the probe in a fixed position. Sensor readings of pH, dissolved oxygen, and temperature for each vessel were monitored and recorded as image annotations. Each collected six-on-one image corresponds to a single “measurement” and was stored as a separate RGB image file (in a lossless PNG format). For each measurement, the sensor readings were used to determine the s_{O_2} for Vessel 1 and Vessel 2. This corresponds to the *measured oxygen saturation*, which was plotted as a function of measurement number. A series of sequential measurements was stored as a *dataset*. The datasets that were analyzed are listed in Table 2.3. For Dataset 1A, the results are in Section 2.4.2.

To analyze RCS, a single numerical value ΔM was computed to characterize factors that affect the ability to distinguish small differences oxygen saturation. This was performed for varied depths and hematocrit levels using Datasets 1B and 1C of Table 2.3. For computing ΔM , the s_{O_2} of one vessel was varied while holding the other constant. The s_{O_2} of Vessel 1 was set to full oxygenation as a *fixed reference vessel*. Vessel 2 s_{O_2} was initially set to 40% and then gradually increased to full oxygenation. When one vessel remains fully oxygenated, this reduces variability in its s_{O_2} and facilitates measuring the oxygenation level at which a loss of contrast is reached. Image colorization was measured from the RGB data (see Section 2.3.5). The lowest measurement number was identified where the difference in *measured image colorization* (as described in Section 2.3.5), between the vessels, is less than a *contrast distinction threshold* ΔC . This was set to an empirically selected threshold value of $\Delta C = 0.5$, where visual distinction is apparent and above the noise floor. The result ΔM was computed by determining, at the measurement number where threshold occurs, the difference in the measured oxygen saturation between the vessels. The procedure was applied to Datasets 1B and 1C, with results in Section 2.4.3.

2.3.4 Penetration depth

The penetration depth for the biologically relevant phantom was investigated by imaging the vessels at two different s_{O_2} levels (Dataset 2 from Table 2.3). The s_{O_2} of Vessel 1 was set to full oxygenation (approx. 99% s_{O_2}), and Vessel 2 was set to very low de-oxygenation (approx. 5% s_{O_2}).

Table 2.3: List of collected datasets. Measurements were performed as indicated parameters were varied.

dataset	s_{O_2} Vessel 1	s_{O_2} Vessel 2	depth	hematocrit
1A	full to 30%	30% to full	15mm	46%
1B	full	40% to full	15mm, 23mm, 30mm	42%
1C	full	40% to full	15mm	42%, 24%, 10%
2	5%	full	14mm to 54mm	42%

The probe was mounted on a linear actuator configured to slide along its elevational axis at a constant speed. Since the vessels are sloped, the acquisition of data at multiple depths could be automated. The geometry of the phantom permitted vessel depth to be varied from approximately 14mm to 53mm. While the linear actuator was active, data was acquired at a constant frame rate. The reference region was set to a vertical size of 5mm and was positioned to encompass the vessels as their depth was varied. The six-on-one composite image maps were collected and stored as individual RGB data files.

The measurements were analyzed in increments of 1mm. At each depth, the measured image colorization was computed and recorded for the OA Combined and OA Total maps, as described in Section 2.3.5. Contrast-to-noise ratio (CNR) is defined by $CNR = \frac{C}{\sigma}$, where C represents the contrast of a target, divided by the standard deviation σ of the background. In statistical mapping using equation (2.6), the color mapping already includes division by σ . Therefore, the measured image colorization, which can be directly associated with C , is also a measure of each target's CNR, because the background standard deviation has already been normalized during the color mapping. In addition, contrast-to-background ratio (CBR) measurements were performed for each vessel using the OA Short and OA Long maps. The formula $CBR = \frac{S-B}{B}$ was used, where S is the peak signal within the vessel, and B is the average background level. Penetration depth corresponds to the point at which CBR is less than a threshold when the vessel can no longer be visualized. The results are presented in Section 2.4.4.

2.3.5 Image analysis

In each dataset, RGB image output was produced by the statistical mapping approach. To analyze this output, an inverse mapping was applied to convert RGB values into a scalar value, which corresponds to the amount of relative colorization of each pixel. Since the hue of RGB colors remains unaltered when RGBA is overlayed with grayscale, this was used to determine the inverse mapping for the f_{RGBA} palette in (2.6). The palettes have a unique hue for each color, so the inverse mapping f_{RGBA}^{-1} exists and is not affected by the grayscale wherever the transparency is non-zero. The hue of each pixel was used with f_{RGBA}^{-1} to determine a real number between k_{min} and k_{max} . OA Relative and OA Combined are mapped from -1 to 1 (from red to green); OA Total is mapped from 0 to 1 (from transparent to yellow). The gray RGB pixels were set to zero, corresponding to transparent areas.

To measure colorization of the vessels in OA Combined, a rectangular window surrounding each vessel was mapped into numerical values, using the inverse mapping described above. The average of this was computed, but only for pixels with mapped values having a magnitude exceeding the median magnitude of the window, which avoided noise by skipping highly transparent pixels. This numerical result, called the *measured image colorization*, was recorded for each vessel and plotted as a function of measurement number.

2.4 RESULTS

2.4.1 *Display of vessels in biologically relevant phantom*

Figure 2.7 shows a composite image of the phantom, captured by an investigational Imagio® system, which consists of the six simultaneously displayed maps described in Section 2.3.2. The circular cross-sections from both vessels are visible in each of the six maps. The depth of the vessels is 15mm, and the field of view (maximum image height) is set to 40mm. Vessel 1 was fully oxygenated to 99% s_{O_2} and appears green. Vessel 2 was oxygenated to 31% s_{O_2} and appears red. In the OA Combined map, colorization is displayed for regions of strong signal in both OA Relative and OA Total maps. Since the vessels have strong hemoglobin and strong relative oxygenation, OA Relative and OA Combined look fairly similar.

In the OA Short and OA Long image maps of Figure 2.7, a different intensity for each vessel is observed because the optical absorption coefficient of blood is wavelength specific and depends on oxygen saturation. Vessel 2, which has a low s_{O_2} (31%), has a low signal in the long wavelength; however, Vessel 2 has strong signal for the short wavelength. Vessel 1, which has high oxygen saturation (99%) has moderately weak signal at the short wavelength, and strong signal in the long wavelength.

2.4.2 *Sensitivity to differences in oxygen saturation*

Varying s_{O_2} of both vessels

In Figure 2.8, the RGB image colorization of the phantom is displayed when s_{O_2} of both vessels is varied using the dual-path perfusion system described in Section 2.3.1. For this figure, the parameters for Dataset 1A, described in Table 2.3, are used. The image colorization was computed from the RGB values of the OA Combined map, as described above. To graphically show the RGB colorization of the vessels from the series of measurements, the region surrounding the vessels are arranged according to measurement number (Figure 2.8b). The line style colors plotted in Figures 2.8a and 2.8c were selected to match the initial RGB measurements in Figure 2.8b. Initially, the s_{O_2} of Vessel 1 is lower than Vessel 2. The measured colorization of Vessel 1 begins negative (red), while Vessel 2 has a positive (green) colorization. As the s_{O_2} levels converge, the colorization becomes weaker, and around measurement number 45 this switches colors as Vessel 1 becomes more oxygenated than Vessel 2.

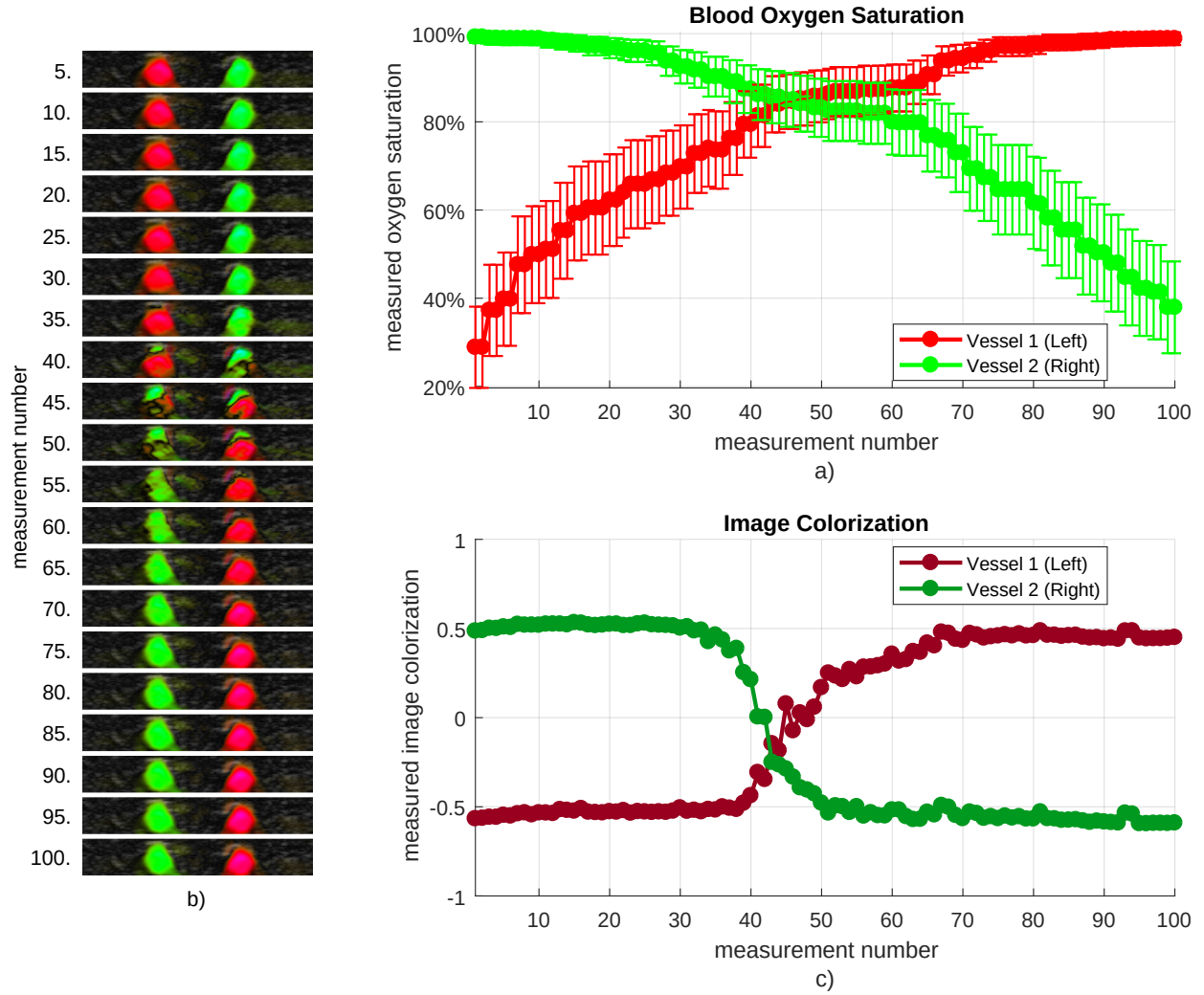


Figure 2.8: Characterization of RGB image colorization as oxygen saturation of Vessel 1 and Vessel 2 is varied in biologically relevant phantom of Figure 2.3. a) The *measured oxygen saturation* is determined from sensor readings. Measurements are sequentially numbered. b) A subregion surrounding the two vessels from the OA Combined image map graphically indicates the displayed colorization for each measurement. c) The *measured image colorization* is determined by mapping the OA Combined RGB data of vessels to a value between -1 and +1. In (a) and (c), the plotted line colors match initial measurements of (b).

Effect of vessel s_{O_2} on relative maps

In Figure 2.9, some of the OA Combined and OA Total image maps used to generate Figure 2.8 are shown at full-size for several s_{O_2} levels. The *oxygen saturation difference* Δs_{O_2} (the difference of measured s_{O_2} between the two vessels) is indicated for each case. For OA Combined, statistical color mapping causes the strongly oxygenated vessel (relative to the background level) to appear green, and the strongly deoxygenated vessel (relative to the background level) to appear red. Signal that is midway between these levels is transparent. As described in Figure 2.5, the colorization adjusts

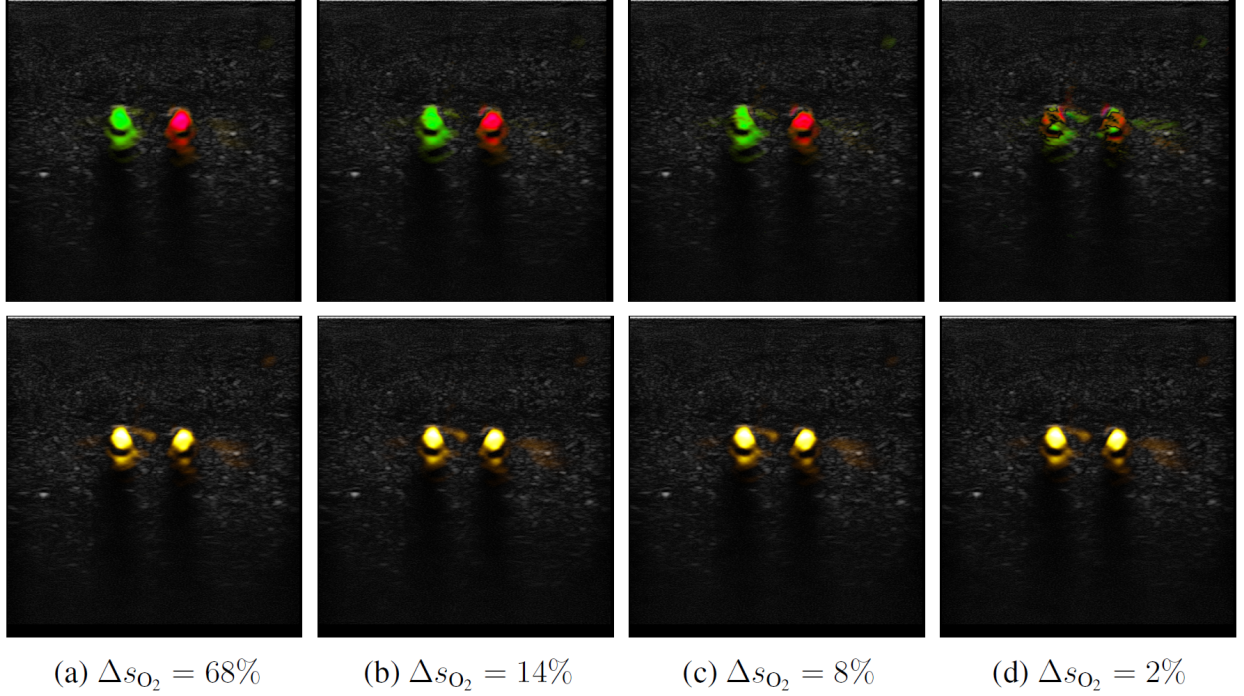


Figure 2.9: Images of PVCP phantom as s_{O_2} is varied. In OA Combined mode (top row), the contrast of colorization between the two vessels depends on the magnitude of the difference in oxygen saturation Δs_{O_2} . In OA Total mode (bottom row), the intensity does not change substantially as s_{O_2} is varied, since c_{tHb} signal is relatively independent of s_{O_2} . Images are collected from Dataset 1A. The image height is 40mm.

dynamically based on the image content to present regions that have significant s_{O_2} differences relative to background levels. In the top row of Figure 2.9, it is observed that with the relative colorization, the resulting color mapped images remain virtually the same until Δs_{O_2} is below a background noise level. Below this level, when the vessels are no longer distinguishable, the colorization represents amplified background variability, since the s_{O_2} levels of both vessels have become nearly the same (Figure 2.9, top right). In the bottom row of Figure 2.9, the corresponding OA Total maps are shown. When s_{O_2} levels are adjusted, the amount of hemoglobin in the blood does not change. Thus, changing the s_{O_2} does not have a substantial impact on the yellow colorization displayed here. Since the visibility in OA Total remains high, characterizing the ability to detect small differences applies only for relative s_{O_2} maps and not for c_{tHb} .

Relative contrast sensitivity measurement

Results from Dataset 1B are illustrated in Figure 2.10, for vessel depth of 15mm and hematocrit of 42%. Vessel 1 was held at a constant fully oxygenated s_{O_2} level of 99%, while Vessel 2 was varied from low oxygenation to full oxygenation. The line style colors plotted in Figures 2.10a and 2.10c match the RGB measurements in Figure 2.10b. Less distinction is observed between the two vessels as their oxygen saturation measurements become closer together. The measurement

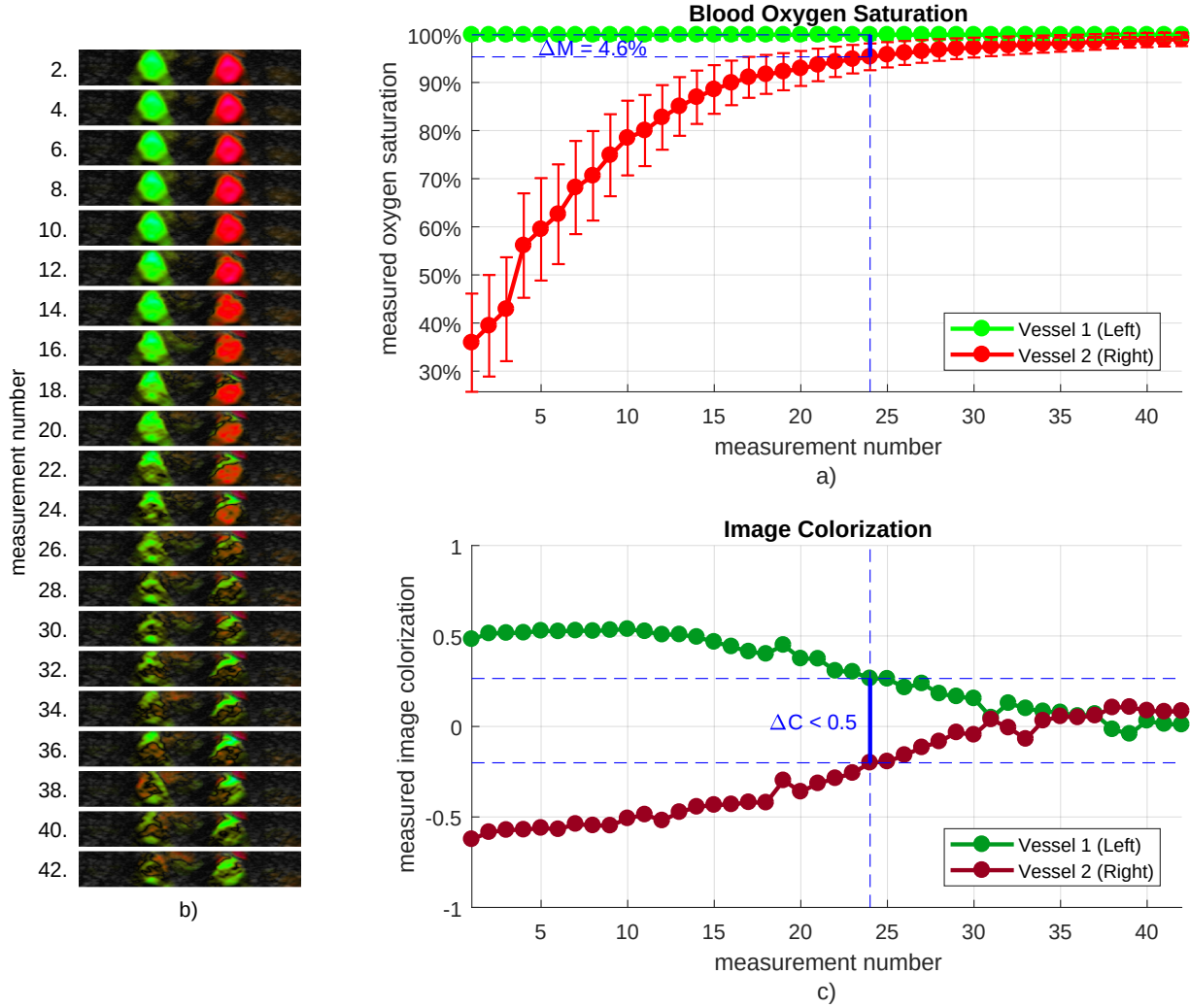


Figure 2.10: Ability to distinguish vessels in biologically relevant phantom. a) Vessel 1 s_{O_2} level is held constant at full oxygenation and Vessel 2 s_{O_2} level is varied. b) OA Combined RGB colorization of Vessel 1 (left) and Vessel 2 (right) by measurement number. High relative s_{O_2} appears green. Low relative s_{O_2} appears red. Mid-range relative s_{O_2} values become transparent. c) The *measured image colorization* as determined from RGB data. In plot c), *contrast distinction threshold* of $\Delta C = 0.5$ is reached at measurement number 24. This occurs when the *measured oxygen saturation difference* ΔM is 4.6%, as shown in a).

Table 2.4: Summary of results for RCS.

$\alpha_{\text{hct}} = 42\%$	
depth	ΔM
15mm	4.6%
23mm	4.7%
30mm	9.7%
(a) Dataset 1B	

depth = 15mm	
hematocrit	ΔM
42%	4.6%
24%	4.5%
10%	7.8%
(b) Dataset 1C	

number at which $\Delta C \leq 0.5$ first occurs was identified, and is indicated in the plots with a vertical blue dotted line. In Figure 2.10, this corresponds with measurement 24. The displayed vessel images (Figure 2.10b) highlight how this corresponds to the last measurement where sufficient color distinction was detected. At this measurement number, the difference in actual measured oxygen saturation ΔM between the two vessels, which corresponds to RCS, was determined as 4.6%.

2.4.3 Varying of vessel depth and blood hematocrit level

RCS measurement

The values for ΔM of Dataset 1B, where depth was varied, are recorded in Table 2.4a. The observed trend is that as depth is increased (from 15mm to 30mm), ΔM is increased (from 4.6% to 9.7%). This occurs because the contrast-to-background ratio (CBR) becomes lower as depth is increased, which increases the s_{O_2} difference required for color distinction. The parameter ΔM is able to assist with characterizing this phenomenon. A similar trend is observed for Dataset 1C in Table 2.4b, where the testing was repeated for varied levels of hematocrit. As hematocrit is decreased (from 42% to 10%), ΔM is increased (from 4.6% to 7.8%). Similar to Table 2.4a, the ΔM increase is because the CBR becomes lower as hematocrit decreases.

Image colorization vs. s_{O_2} difference

From the datasets, we can also examine the difference in image colorization as a function of Δs_{O_2} , the difference in oxygen saturation. This is plotted in Figure 2.11. The threshold where $\Delta C = 0.5$ is indicated by a horizontal dotted line. The curves, as depth is varied for Dataset 1B, are shown in Figure 2.11a. In Figure 2.11b, the trend is plotted for the three hematocrit levels from Dataset 1C. From these curves, the value of ΔM can be derived by finding the x-coordinate where each curve intersects the dotted line. This also characterizes RCS by illustrating the relationship between Δs_{O_2} and ΔC , and provides information about how ΔM changes with the threshold for ΔC . In addition, Figure 2.11 illustrates that for cases where CBR is higher (15mm depth, 42% hematocrit), the ability to distinguish the vessels based on image colorization increases. It also shows that the maximum difference in image colorization plateaus beyond a certain level of s_{O_2} , and this level is greater at high CBR. It is seen that below $\Delta C \approx 0.5$, the curves have greater variability, which illustrates why this cutoff level was relevant.

The effect of varying depth on CBR is illustrated visually in Figure 2.12. OA Combined and OA Total maps are shown for different imaging depths, when the vessels are held at constant s_{O_2} levels. At 15mm depth, the intensity of the background is low. Background intensity visually becomes greater when the vessels are imaged at 23mm, and is substantially increased when the vessels are at 30mm. The signal received from a vessel becomes weaker as its depth is increased. However, since the reference region encompasses the vessels, the statistics for color mapping automatically maximize the contrast of the vessels. This means that when the color mapping is

targeted to deep vessels, the colorization scales automatically to visualize these weaker signals. As a result, when the vessels are imaged at 30mm depth, amplification of the near-field background is observed in the image, however the background for region surrounding the vessels is transparent. This is what is desired for the analysis described above, where the RGB values for the region surrounding the vessels determine the image characterization.

2.4.4 Penetration depth

The results of penetration depth testing from Dataset 2 are shown in Figure 2.13. Figure 2.13a demonstrates that both targets are visible in OA Combined map to depths of around 48 mm. In Figure 2.13b, both targets are visible in OA Total beyond 42mm, while Vessel 1 remained visible to around 48mm.

In Figure 2.13c and Figure 2.13d, the CBR measurement was used to determine the penetration depth of the targets at each wavelength. A CBR threshold value of 1.5 was used, which corresponds to when the targets could be distinguished from the background. Below this threshold, it was difficult to visualize the vessels clearly. In Figure 2.13c, for OA Short (757 nm), the oxygenated target maintains $CBR > 1.5$ up to a depth of 32 mm, while the deoxygenated target maintains $CBR > 1.5$ up to a depth of 42 mm. In Figure 2.13d, for OA Long (1064 nm), the oxygenated target maintains $CBR > 1.5$ up to a depth of 48 mm, while the deoxygenated target did not have significant contrast even at the minimum depth of 14mm. Therefore, the penetration depth for OA Short (757 nm), which strongly detects HbR, is determined to be 42 mm. For OA Long (1064nm), which strongly detects HbO₂, the penetration depth was determined to be 48 mm.

2.5 DISCUSSION

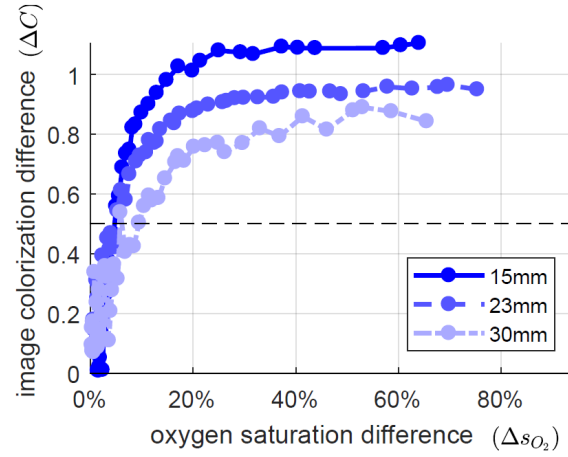
2.5.1 Characterization of relative s_{O_2} and c_{tHb} with dual-path flow system

We investigated the use of a dual-path perfusion flow system to perform device characterization for statistical color mapping of relative s_{O_2} and c_{tHb} . Controlling the s_{O_2} level of two independent vessels permits determining the ability to resolve differences in s_{O_2} level.

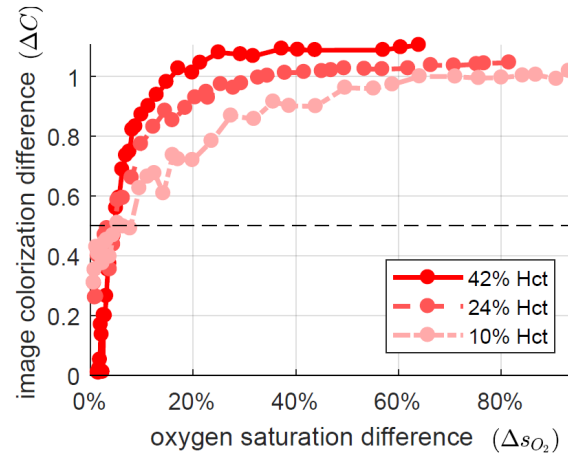
In a single-vessel configuration, which was described in previously published approaches [50] [54], the device characterization would be difficult for several reasons: i) First, the signal intensity and oxygenation level of the background medium are not adjustable. If the relative colorization of a single vessel was compared to the background, the background would serve as a fixed reference. When the s_{O_2} level of the vessel reached that of the background, the vessel would become transparent according to the color map of Figure 2.6. The transparency would be a problem for analyzing the amount of image colorization. ii) The background produces a relatively weak OA signal, whereas a vessel can produce a strong signal from blood. The CBR of the background is weak (by definition it is equal to zero), whereas for a vessel it is higher. Therefore, using the phantom's background as a reference point for a quantitative s_{O_2} level, which has an inherently low CBR, would be problematic. iii) The homogeneity of the phantom

background causes it to predominantly emit low-frequency OA signal. This tends to be filtered out by the system transfer-function response, so the DC portion of the received signal is blocked. Therefore, the absence of vascularity makes it difficult to use the phantom's background as a quantitative reference point for s_{O_2} .

On the other hand, the two-vessel configuration permits the ability to characterize mappings of relative s_{O_2} and c_{tHb} by examining the difference between each vessel as they are simultaneously imaged. This avoids the issues of the single-vessel configuration described above.



(a)



(b)

Figure 2.11: Image colorization difference ΔC is compared to oxygen saturation difference Δs_{O_2} . (a) Depth is varied at fixed hematocrit level of 42%. (b) Hematocrit level is varied at fixed depth of 15mm. The horizontal dashed line corresponds to threshold $\Delta C = 0.5$.

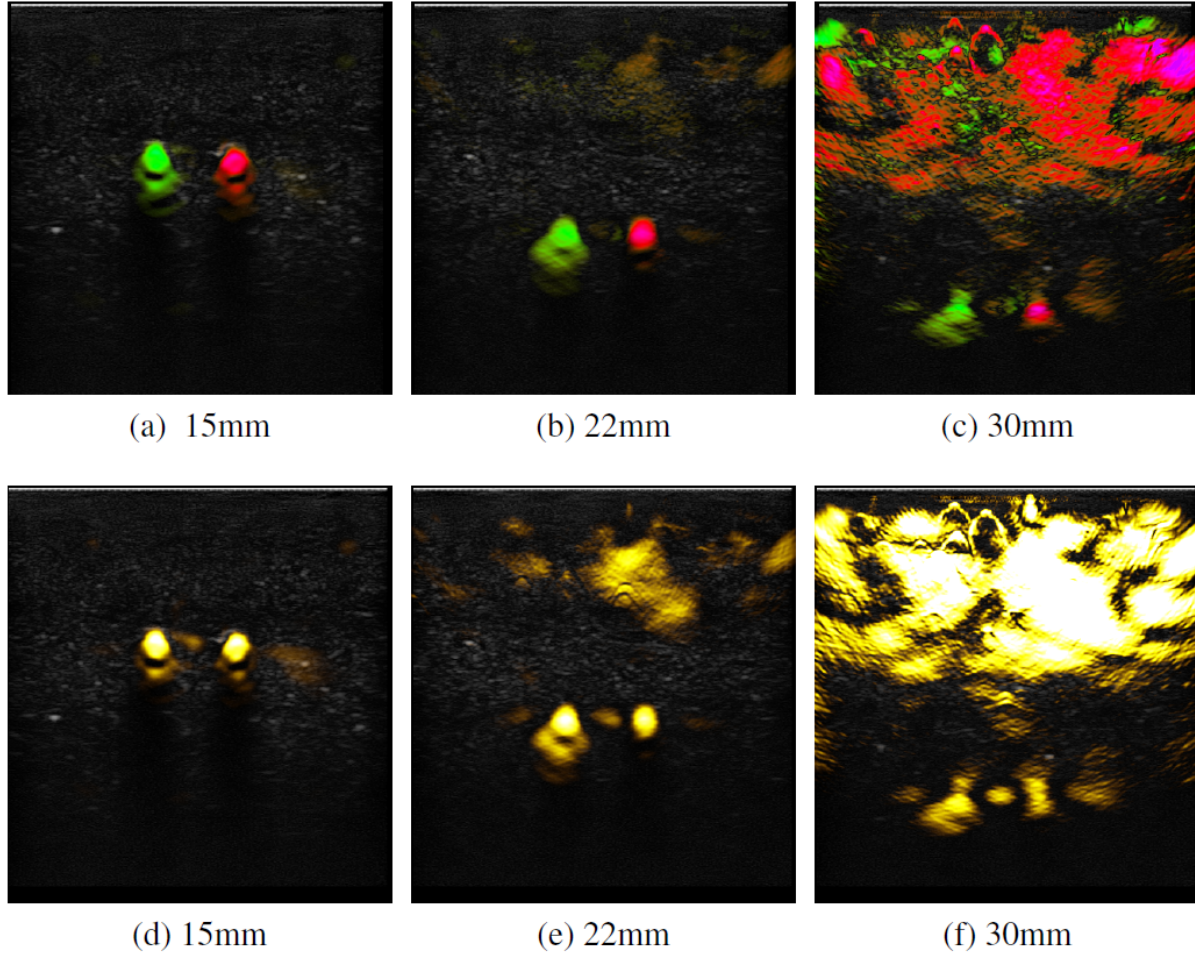


Figure 2.12: OA Combined and OA Total maps as depth is varied. Vessel 1 (left, oxygenated) has constant s_{O_2} of 99%. Vessel 2 (right, de-oxygenated) has constant s_{O_2} of 5%. OA Combined maps are shown in a), b) and c). OA Total maps are shown in d), e) and f). The contrast-to-background ratio (CBR) of the vessels is reduced as depth increased. Selecting a reference region to visualize deep vessels causes an increase of statistical gain parameter σ , which amplifies near-field background while contrast of targets is maximized. The region surrounding vessels is used for analysis.

2.5.2 Differences between phantoms and breast tissue

When performing characterization on a phantom, there are several potential limitations in interpreting the results due to differences between phantoms and breast tissue. However, phantom-based results can be used to make some general interpretations about relative color mapping in tissue.

When performing characterization, both targets in the phantom were imaged at approximately equal depth, and due to the homogeneous material properties, the targets received nearly equal fluence, and had nearly equal acoustic propagation paths for measurement. This represents an ideal scenario for performing controlled characterization, as the independent variables of the blood can be isolated based on the amount of signal generated by either target.

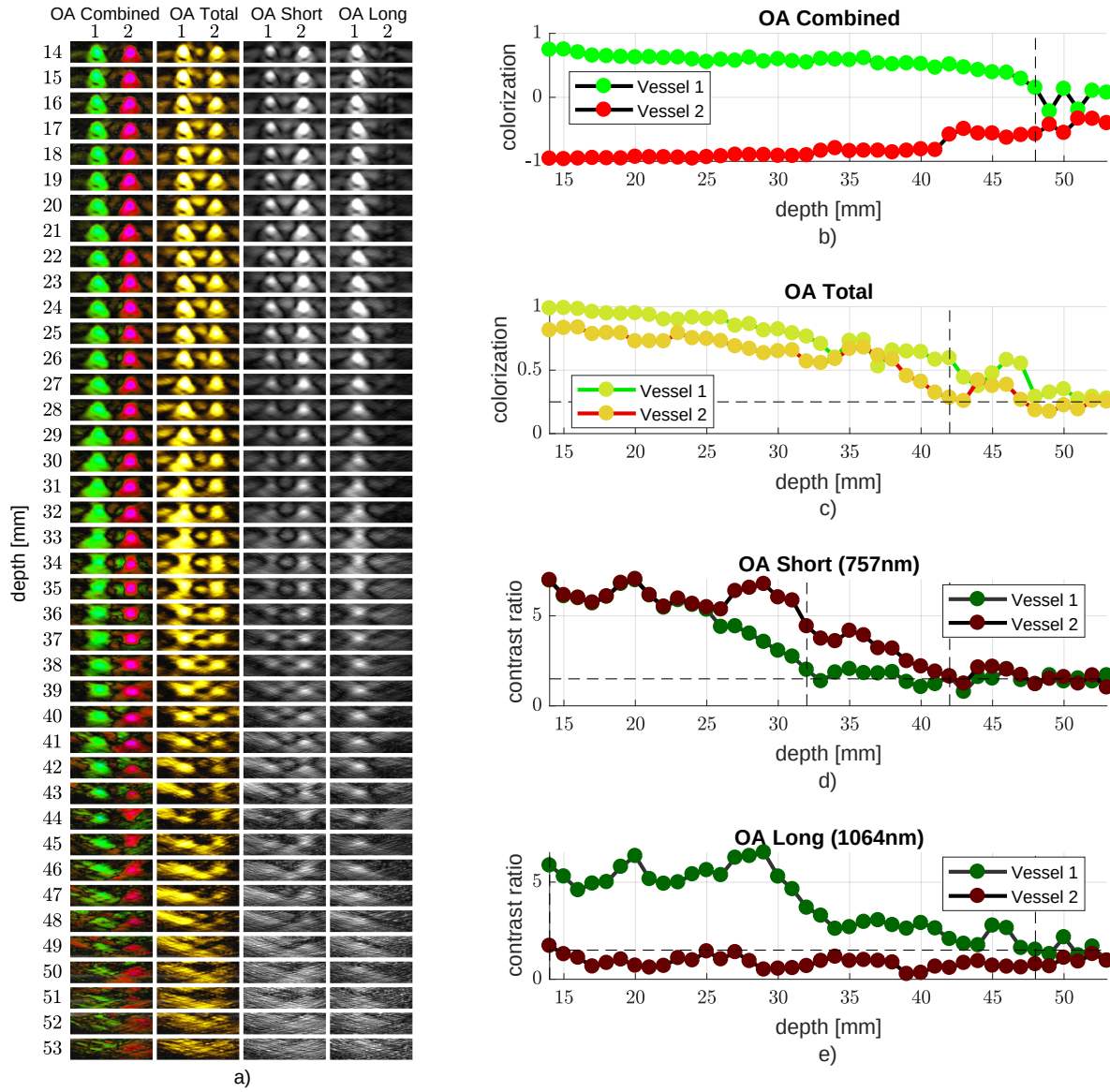


Figure 2.13: Vessel contrast as depth is varied. Vessel 1 (oxygenated) has constant s_{O_2} of 99%. Vessel 2 (de-oxygenated) has constant s_{O_2} of 5%. a) Image maps are displayed for both vessels. b) OA Combined map colorization for relative s_{O_2} is plotted as a function of depth. Vessel distinction is present to 48mm. c) OA Total map colorization for c_{tHb} as a function of depth. At 42mm, signal from Vessel 2 reaches visibility threshold, while Vessel 1 remains above threshold until 48mm. d) Contrast-to-background (CBR) measurement of OA Short (757nm) image map, which presents signal from deoxygenated blood. Vessel 1 is above CBR threshold to 32mm and Vessel 2 remains above threshold to 42mm. e) CBR measurement of OA Long (1064nm), which presents signal from oxygenated blood. Vessel 1 remains below CBR threshold, while Vessel 2 remains above threshold to 48mm penetration depth.

Conversely, biological tissue has increased non-homogeneity of optical and acoustical properties compared to the phantom, which can impact signal generation. As a result, tissue may have decreased CBR compared to the phantom. In addition, benign or malignant lesions may occur at different depths and have different hematocrit levels. By definition, the CBR increases with OA signal strength, which is impacted by depth (equation 2.4) and hemoglobin concentration (equation 2.3). Therefore, this situation may lead to reduced CBR during imaging for some lesions. Furthermore, while the phantom only has two targets, acoustic interference from other sources or targets in tissue can lead to decreased CBR. A decrease in CBR may reduce penetration depth. This may also impact relative colorization, since it was demonstrated in Section 2.4.3 that RCS is impacted by the CBR. When CBR is reduced, for example at increased depth, or at decreased hematocrit level, the ΔM increases (as shown in Figure 2.11). In this case, a greater difference in s_{O_2} between each vessel would be required to maintain distinguishable colorization.

Other factors can also impact the RCS and ability to display relative s_{O_2} . To illustrate this, consider a perturbation $\Delta\Phi$ from a modeled fluence distribution Φ . From equation (2.1), the generated OA signal depends on Φ . Variability of optical properties or spatial non-homogeneity, which may be present in tissue, tends to increase $\Delta\Phi$ for targets being imaged. If $\Delta\Phi$ is increased, then ΔM , which represents the difference in actual s_{O_2} values to distinguish the targets, may also increase. With the phantom characterization apparatus, at either specific wavelength, both targets receive nearly equal fluence, and perturbation from the modeled Φ is assumed to be small. However, in a scenario where targets receive a greater uncompensated $\Delta\Phi$, such as in tissue, this may correspond with greater ΔM . In addition, in tissue, the Grüneisen parameter Γ can vary spatially, leading to additional perturbation in signal generation. For tissue, it is assumed that there is small variability in Γ . Spatial variability in Γ can lead to increased ΔM . Likewise, spatial variation in hematocrit level could produce a similar effect.

2.5.3 Visualizing relative s_{O_2} and c_{tHb} with statistical color mapping

In statistical color mapping, which performs relative colorization of s_{O_2} and c_{tHb} (as described in Section 2.3.2), the goal is to maximize the contrast of a target or lesion compared to background tissue, rather than to measure precise numerical values of a parameter. Colorization is determined dynamically, to highlight areas that are *relatively* more significant compared to others. The approach is considered *qualitative* because numerical measurements of s_{O_2} and c_{tHb} are not conveyed with the generated RGB maps.

One advantage for statistical color mapping is the ability to display relative s_{O_2} and c_{tHb} when quantitative parameter estimates could have offset and scaling that is difficult to determine in advance. Specifically, the procedure can help compensate for some variability in tissue opto-acoustic properties and fluence distribution that impact OA signal generation, as described in Section 2.5.2. To dynamically maximize contrast, colorization is determined relative to a background reference region, by computing μ and σ in equation (2.6). This tends to cancel out perturbation to parameters that affect signal generation, when stationary over the reference region.

For example, if the assumed parameters and coefficients contributing to equations (2.1) or (2.A.3) are offset or scaled from their actual values (e.g., by stronger signal from one wavelength), then μ and σ of the estimated s_{O_2} and c_{tHb} quantities will also be offset and scaled, at least to a first approximation. However, with statistical mapping, any offset and scaling to the distribution of parameter estimates will be dynamically compensated, relative to the background. In other approaches, where quantitative parameter estimates are directly output or mapped to a fixed color, variations in fluence distribution and opto-acoustic properties may result in the displayed color or output being shifted.

For purposes of diagnostic imaging in tissue, the statistical reference region used to compute μ and σ (described in Section 2.3.2) is commonly set to encompass the entire mid-field of the image (e.g. from 5mm to 30mm). This is selected to provide and maximize statistical contrast of the image based on properties of the full image region. This is applicable when imaging tissue, which can have more than two vessels as configured in our phantom. By using the statistics of this region, the mapping detects areas of contrast that appear as outliers from background levels, which presents information about the relative spatial distributions of c_{tHb} and s_{O_2} . In clinical studies, this was demonstrated to be an effective method to visualize breast lesions compared to the background tissue [7], [9], [13], [14].

2.5.4 *Application of relative s_{O_2} and c_{tHb} for OA/US clinical breast diagnosis*

Several clinical studies for breast cancer diagnosis [7]–[15] have examined the ability to distinguish benign from malignant lesions using relative OA/US maps generated with an investigational Imagio® breast imaging system. For radiological assessment during these studies, the OA/US maps were formatted as a six-on-one composite image, similar to Figure 2.7, which displays ultrasound, OA Total, OA Combined, OA Relative, OA Short, and OA Long. Results from a Feasibility study were initially reported by Zalev et al. [13]–[15] and Otto et al. [71]. In a Pilot study of 100 subjects, Neuschler et al. [8] found that using the relative OA/US technique to assess images resulted in downgrading of benign masses and upgrading of malignant masses compared with conventional ultrasound. In a multi-center OA/US study of 209 subjects, Menezes et al. (2018) [9] also found that certain benign masses suspicious for cancer could potentially be downgraded to a category where biopsy is not required. Butler et al. [10] reported on a correlation between relative OA/US image features and the histo-pathology of benign and malignant lesions. Menezes et al. (2019) reported that OA/US might also be useful to differentiate breast cancer molecular subtypes [11]. A subsequent multi-center Pivotal study (Neuschler et al. [7]) consisted of 2105 subjects from 16-sites, where seven blinded and independent radiologists assessed 1079 benign and 678 malignant breast masses. In the study, relative OA/US was found to exceed diagnostic specificity of conventional ultrasound by 14.9%.

These results demonstrate the diagnostic potential of relative OA/US maps for clinical breast imaging. Accordingly, there is a practical significance for characterizing relative s_{O_2} and c_{tHb} maps for this application.

2.5.5 Other OA visualization approaches for clinical breast imaging

In addition to the studies listed above, other visualization approaches for OA have been investigated for clinical breast imaging. Kitai et al. (2014) [29] performed comparison of OA with MRI. Asao et al. (2016) [30] investigated simultaneous acquisition of OA and ultrasound. Toi et al. (2017) [31] described producing high-resolution vascular images using a 3D tomographic full-breast imaging device, where a relative index, called the S-factor, was used to display qualitative s_{O_2} maps. Kruger et al. [32], [33] developed a 3D tomographic OA breast imaging device capable of imaging vessels in breast tissue at 250 μm resolution using a single optical wavelength. Klosner et al. [34] also developed a system for high-resolution 3D imaging of breast vasculature. A volumetric 3D hand-held probe for OA imaging is described by Dean-Ben et al. (2016) [35]. Li et al. (2015) [36] investigated lesion visibility from c_{tHb} and s_{O_2} contrast. Lin et al. (2018) [37] formed colorized 3D images of arteries and veins by analyzing heartbeat information and compared this to full-breast images with depth-encoded colorization. Garcia-Urbe et al. [42] used OA to image sentinel lymph nodes in breast tissue. Heijblom et al. [38]–[40] and Manohar et al. [41] investigated lesion visibility and the appearance of masses in OA. In addition, several review papers for OA breast imaging have compared the visualization approaches of various imaging devices, along with the corresponding tumors features that were clinically detected [1]–[5], [12], [19], [20], [43].

2.5.6 Relationship of statistical mapping with quantitative imaging approaches

Relative OA/US imaging with statistical color mapping is different from *quantitative* imaging approaches. In quantitative imaging, numerical measurements of physical parameters such as s_{O_2} and c_{tHb} are displayed directly, or linked to colorization, and therefore the numerical quantities can be evaluated during clinical assessment. This involves determining accurate measurement of numerical values for tissue chromophore levels or other parameters. A review of quantitative OA imaging techniques by Cox et al. [72] describes implementation and the associated challenges with these approaches in detail. Quantitative numerical values are difficult to calibrate due to variability of tissue properties between subjects.

A distinction between statistical mapping and quantitative approaches is illustrated by the RGB image characterization of Section 2.3.3, where measured image colorization was used instead of the s_{O_2} level. In particular, to quantitatively determine s_{O_2} or c_{tHb} from a statistically mapped RGB image, the values of σ and μ in (2.6) must be known (to uniquely relate the color palette to the numerical parameter values). However, since σ and μ are internal variables that are not provided as output, this is under-determined, and values were mapped between $k_{\min}$ and $k_{\max}$. In this sense, only the relative spatial information is accessible from the statistically mapped RGB output.

2.6 CONCLUSION

We have presented a method for characterizing colorized opto-acoustic image maps that display spatial information regarding relative blood oxygen saturation and hemoglobin in tissue. A biologically relevant PVCP based phantom was constructed to mimic the optical and acoustical properties of breast tissue. The phantom comprised two independently oxygenated vessels filled with bovine blood. A statistical color mapping procedure was used to generate RGB colorization of opto-acoustic signal. A technique was proposed to characterize the ability to resolve small differences in s_{O_2} when using maps with relative colorization. In the PVCP phantom, it was measured that distinguishing a first vessel from a second vessel required a s_{O_2} difference of 4.6%, when imaged at 15mm depth and at 42% hematocrit. By analyzing the effects of varying vessel depth and hematocrit level, it was determined that a reduction of CBR reduces the ability to distinguish s_{O_2} between vessels. In addition, by analyzing the color mapping approach, we examined how the spatial distributions of relative s_{O_2} and c_{tHb} may potentially be used during clinical assessment to visualize differences between benign and malignant lesions for breast cancer diagnosis. Future work involves performing further device characterization and developing techniques to improve visualization of diagnostic imaging features.

2.A APPENDIX

2.A.1 Optical absorption of biological tissue

In biological tissue, absorption can be modeled as a mixture of HbR, HbO₂, melanin, and several other less significant chromophores (e.g., water and lipids) [59]. At optical wavelength λ , the overall absorption coefficient $\mu_a(\lambda)$ is a weighted combination of the i -th chromophore's absorption $\mu_{a,i}(\lambda)$ times its *volume fraction* $f_{v,i}$. For example,

$$\begin{aligned}\mu_a(\lambda) = & f_{v,\text{HbO}_2} \times \mu_{a,\text{HbO}_2}(\lambda) + f_{v,\text{HbR}} \times \mu_{a,\text{HbR}}(\lambda) + f_{v,\text{melanin}} \times \mu_{a,\text{melanin}}(\lambda) \\ & + f_{v,\text{water}} \times \mu_{a,\text{water}}(\lambda) + f_{v,\text{lipids}} \times \mu_{a,\text{lipids}}(\lambda) + \dots\end{aligned}$$

Equivalently, this can be written as a summation of the mass concentration c_i times the *optical extinction coefficient* $\varepsilon_i(\lambda)$. Thus,

$$\mu_a(\lambda) = \sum_i f_{v,i} \times \mu_{a,i}(\lambda) = \sum_i c_i \times \varepsilon_i(\lambda).$$

Commonly, the optical absorption coefficient $\mu_a(\lambda)$ is computed by considering absorption only from hemoglobin, since melanin is present mainly in the epidermal layer, and the other chromophores are assumed negligible. Therefore, at position $\mathbf{x}$, the absorption can be approximated as

$$\mu_a(\lambda, \mathbf{x}) = c_{\text{HbO}_2}(\mathbf{x}) \times \varepsilon_{\text{HbO}_2}(\lambda) + c_{\text{HbR}}(\mathbf{x}) \times \varepsilon_{\text{HbR}}(\lambda). \quad (2.A.1)$$

This expression can also be grouped in terms of s_{O_2} and c_{tHb} . By substituting (2.2) into (2.A.1), this results in equation (2.3), which has a linear dependence of $\mu_a(\lambda)$ on c_{tHb} .

2.A.2 Computation of c_{HbO_2} and c_{HbR}

To determine c_{HbO_2} and c_{HbR} from transducer measurements, equation (2.1) must be inverted, which relies on the wavelength-specific optical absorption of Appendix 2.A.1. For a tissue sample with *known* hemoglobin concentrations, the generated OA pressure can be obtained by combining equation (2.1) with equation (2.A.1). For wavelength λ , and position $\mathbf{x}$, this is

$$p_0(\lambda, \mathbf{x}) = \Gamma(\mathbf{x}) \times \Phi(\lambda, \mathbf{x}) \times [c_{\text{HbO}_2}(\mathbf{x}) \times \varepsilon_{\text{HbO}_2}(\lambda) + c_{\text{HbR}}(\mathbf{x}) \times \varepsilon_{\text{HbR}}(\lambda)].$$

Since multiple optical wavelengths are used, this is repeated for each wavelength. It is convenient to write this in matrix form. If two wavelengths are used, i.e. $\lambda_1 = 757\text{nm}$ and $\lambda_2 = 1064\text{nm}$, this becomes

$$\underbrace{\begin{bmatrix} p_0(\lambda_1, \mathbf{x}) \\ p_0(\lambda_2, \mathbf{x}) \end{bmatrix}}_{\mathbf{p}(\mathbf{x})} = \Gamma(\mathbf{x}) \underbrace{\begin{bmatrix} \Phi(\lambda_1, \mathbf{x}) & 0 \\ 0 & \Phi(\lambda_2, \mathbf{x}) \end{bmatrix}}_{A(\mathbf{x})} \underbrace{\begin{bmatrix} \varepsilon_{\text{HbO}_2}(\lambda_1) & \varepsilon_{\text{HbR}}(\lambda_1) \\ \varepsilon_{\text{HbO}_2}(\lambda_2) & \varepsilon_{\text{HbR}}(\lambda_2) \end{bmatrix}}_{\mathbf{E}} \underbrace{\begin{bmatrix} c_{\text{HbO}_2}(\mathbf{x}) \\ c_{\text{HbR}}(\mathbf{x}) \end{bmatrix}}_{\mathbf{c}(\mathbf{x})}.$$

For each position $\mathbf{x}$, this can be written more compactly as

$$\mathbf{p} = A\mathbf{c}. \quad (2.A.2)$$

When imaging tissue, the *unknown* concentrations of $c_{\text{HbO}_2}(\mathbf{x})$ and $c_{\text{HbR}}(\mathbf{x})$, which are represented by $\tilde{\mathbf{c}}$, can be solved by inverting the 2×2 matrix for A in equation (2.A.2). Thus,

$$\tilde{\mathbf{c}} = A^{-1}\tilde{\mathbf{p}}. \quad (2.A.3)$$

Here, $\tilde{\mathbf{p}}$ represents a map of the initial pressure $p_0(\lambda, \mathbf{x})$, which has been reconstructed by an imaging algorithm using data recorded from transducers, because $\mathbf{p}$ from equation (2.A.2) is not directly measured.

To compute estimates of $s_{\text{O}_2}(\mathbf{x})$ and $c_{\text{tHb}}(\mathbf{x})$ for OA images, the values of $c_{\text{HbO}_2}(\mathbf{x})$ and $c_{\text{HbR}}(\mathbf{x})$ can be substituted into equations (2.2a) and (2.2b).

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2.S SUPPLEMENTAL MATERIAL

Accuracy of s_{O_2} measurement using oxygen dissociation curves

In this section, we analyze the accuracy of measuring the oxygen saturation level of blood using oxygen dissociation curves. The model described by Dash et al. [69] relates s_{O_2} level of blood to five dependent variables: pH, temperature, level of DPG (2,3-diphosphoglycerate), partial pressure of carbon-dioxide (pCO₂), and dissolved oxygenation (DO). As described in Section 2.3.1, sensors were used to record measurements of pH level, temperature, and DO in the blood, according to the schematic of Figure 2.4. An analysis of measurement accuracy was performed by computing the difference between the maximum and minimum s_{O_2} values resulting from the Dash et al. model [69], when applied to a set of accuracy values for each sensor, as summarized in Table 2.S.1. The analysis investigated all possible permutations within the assumed measurement ranges (32 possibilities arise by selecting the upper or lower range boundaries from the five dependent variables: pH, temperature, DPG, pCO₂, and DO). The pH measurement accuracy, which is based on the specification of our pH meter (Denver Instruments, Model: UB-10), was assumed to be ± 0.1 ; the accuracy of the DO sensor (Oakton, Model: DO-450) was assumed to be ± 0.1 ; for temperature, which was measured using the same sensor, the accuracy was assumed to be $\pm 0.5^\circ\text{C}$. Nominal operating values for pH and temperature were assumed to be 7.4 and 23°C . The DO, which corresponds to the partial pressure of oxygen (pO₂) was analyzed from 0 to 120 mmHg. A large range of values was used for pCO₂, which was assumed to be anywhere from 0 to 80mmHg, since carbon-dioxide adjustment is used to control pH. A large range was also used for DPG concentration, which was assumed to be from 1mM to 4mM, based on clinically relevant ranges.

The hemoglobin dissociation curves describe how s_{O_2} varies as a function of pO₂. The maximum and minimum curves, computed by varying parameters based on accuracy tolerance of Table 2.S.1, with all 32 possible permutations for boundary ranges, are shown by the dotted lines in Figure 2.S.1. The average hemoglobin dissociation curve is shown as a dark line, with error bars coinciding on the dotted lines. The error is highest near 10 mmHg pO₂.

In Figure 2.S.2, the error in measurement accuracy is plotted as a function of actual s_{O_2} , which is obtained by computing the difference of the two dotted lines in Figure 2.S.1. The measurement error is greatest at around 50% actual s_{O_2} and is most accurate near 0% and 100% s_{O_2} . This can also be seen in Figure 2.S.1, where the size of the error bars is small on the left and right sides

Table 2.S.1: Accuracy assumptions for sensor readings

Parameter	Nominal Value for Analysis	Accuracy
pH	7.4	± 0.1
pCO ₂	40mmHg	± 40
temperature	23°C	± 0.5
DPG	2.5mM	± 1.5
pO ₂	0 - 120 mmHg	± 0.1

of the curve where it plateaus. For the assumed ranges of measurement accuracy, Figure 2.S.2 indicates that if the measured s_{O_2} of blood is around 50%, then the actual value will be accurate to within $\pm 15\%$. If measured s_{O_2} of blood is above 80%, the accuracy will be within 9%. If measured s_{O_2} of blood is above 90%, the accuracy will be within 5%; and if measured s_{O_2} of blood is above 95%, the accuracy will be within 2%. We observe that the measurement accuracy resulting in Figure 2.S.2 is approximately parabolic. To generate error bars, this is represented by the function

$$a(1 - ((x - 50)/50)^2) + b,$$

where x represents the s_{O_2} level, and a and b are fitted parameters. When computing error bars, the nominal operating values for pH and temperature were at 7.4 and 23 °C. It is assumed that when performing measurements, a small offset from these nominal operating values has a linear effect, and does not impact the size of the error bars. In other words, we are assuming that the magnitude of the computed error bars is not a function of pH and temperature. Increasing the amount of error beyond the ranges of Table 2.S.1 would, of course, result in greater s_{O_2} measurement error. However, in this situation, the lowest accuracy in measuring s_{O_2} would still occur at values near the s_{O_2} midpoint of 50%. For this reason, when performing relative measurements with the dual-vessel system, it was found that accuracy could be increased by maintaining a reference vessel fixed at 100% s_{O_2} , which has the lowest amount of uncertainty. In experiments where s_{O_2} is varied, an offset in one of the independent variables could result in oxygen dissociation curves being shifted to one direction. For increased accuracy, commercial meters calibrated to determine s_{O_2} directly from blood could also be used. In measurements performed by Vogt et al.(2018; 2019), a clinical grade CO-oximeter (Accriva Diagnostics, Model: Avoximeter 4000) was used as reference device for providing gold standard measurements. For our article, s_{O_2} was computed based on measurements from sensors using oxygen dissociation curves without external oximeter. Based on the accuracy analysis described in this supplemental section, we are able to predict uncertainty for the experiments using the dual-vessel system (Datasets 1B, 1C, 2 of Table 2.3). Therefore, by maintaining one reference vessel fixed at 100% s_{O_2} , the process is designed to improve accuracy and reduce uncertainty in relative s_{O_2} measurement.

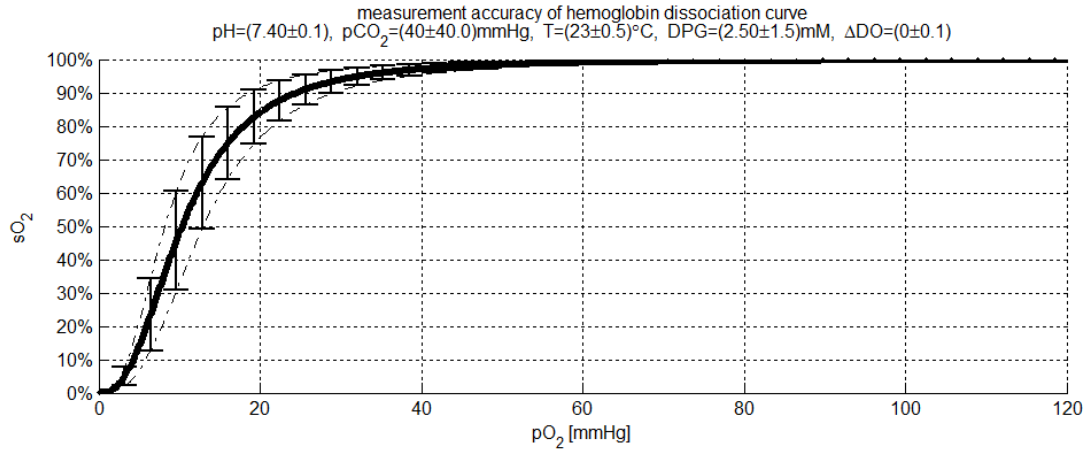


Figure 2.S.1: Measurement accuracy of hemoglobin dissociation curve. Dotted lines indicate maximum and minimum levels due to combined variations of parameter tolerance ranges

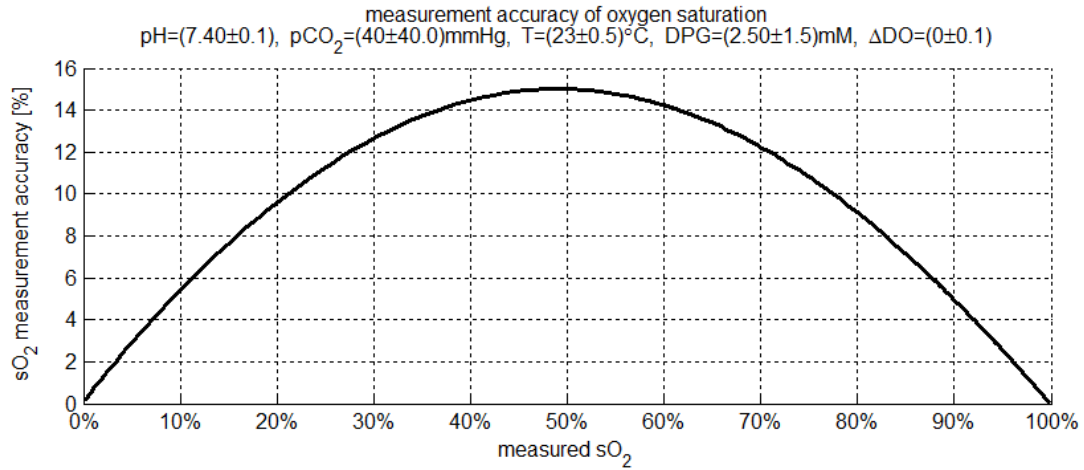


Figure 2.S.2: Measurement accuracy of oxygen saturation as a function of actual oxygen saturation. A low value indicates that measurement is more accurate, thus the measurement error peaks around 50% s_{O_2} and is highly accurate near 0% and 100% s_{O_2} .

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AUTHOR CONTRIBUTIONS FOR THIS CHAPTER

JZ was the primary author of this work (Chapter 2), generated and processed the results, performed analysis of the results, performed literature review, specified phantom geometry and experiments, and developed the algorithm used to generate OA images, including statistical color mapping, time-domain OA signal processing, image reconstruction and post-processing. LMR contributed to editing this work, contributed to analysis, and performed supervision of experiments. BAC supervised portions of this work, is the software development lead for Imagio and contributed to algorithms used for statistical color mapping and OA processing. JH developed the apparatus used to oxygenate blood, performed mechanical engineering for the phantom, contributed to data collection and was instrumental to carrying out the experiments. EC, AB, and XRS were instrumental to carrying out the experiments. GLM provided clinical interpretation of breast lesions. CAA performed laser safety analysis and contributed to specifying phantom optical properties. SCM supervised portions of this work and contributed to analysis. AAO contributed essential feedback to carrying out the experiments, development of phantoms, and was instrumental in the early development of Imagio. MCK supervised portions of this work and contributed to development and specification of the experiments.

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ABSTRACT

Simulation involves predicting responses of a physical system. In this article, we simulate opto-acoustic signals generated in a three-dimensional volume due to absorption of an optical pulse. A separable computational model is developed, which splits processing into two steps, permitting an order-of-magnitude improvement in computational efficiency over a non-separable model. The simulated signals represent acoustic waves, measured by a probe with a linear transducer array, in a rotated and translated coordinate frame. Light is delivered by an optical source that moves with the probe's frame. A spatio-temporal impulse response for rectangular-element transducer geometry is derived using a Green's function solution to the acoustic wave equation. The approach permits fast and accurate simulation for a probe with arbitrary trajectory, which is useful for modeling free-hand acquisitions. For a 3D volume of n^3 voxels, computation is accelerated by a factor of n . This may potentially have application in opto-acoustic imaging, where clinicians visualize structural and functional features of biological tissue for assessment of cancer and other diseases.

3.1 INTRODUCTION

Acoustic waves are generated when light heats optically absorbing materials. In biological tissues, laser pulses produce strong opto-acoustic signals from blood and other optical sources. To permit visualization of cancer and other diseases, transducer arrays must detect the opto-acoustic signals to form images. Rapid simulation may be required during image formation to solve an inverse problem. Simulations are also used for analysis purposes. Accurate simulation of the physics of a system, including modeling of transducer elements and their impulse responses, is critical to avoid distortion in certain applications. However, the processing time required for 3D simulation, especially when an accurate transducer model is used, can be a limiting factor. Here we provide a mathematical derivation and approach for performing fast opto-acoustic simulation of a 3D volume for a linear array with rectangular elements. In this approach, a forward (and/or adjoint) operator is computed in the time-domain using a *separable cascade*. We prove that a non-separable 3D Green's function model of the system response is equivalent to a cascaded series of two perpendicular 2D operations, even when the optical energy distribution, and spatial impulse response of the transducer's rectangular aperture are included. This can greatly improve the computational efficiency. For a linear array, time-domain data is computed efficiently due to shift-invariance in the cascaded operation. Furthermore, the linear array can have arbitrary position and orientation, relative to the 3D volume of opto-acoustic sources. This facilitates simulating multiple frames of data when the linear array moves along an arbitrary trajectory to record data for several laser pulses. In clinical imaging, this type of motion occurs during free-hand scanning with a probe at the surface of a subject's skin. Accordingly, we plan to incorporate the proposed technique towards improving image quality for opto-acoustic image reconstruction.

3.1.1 Outline

In Section 3.1, we introduce the context of fast opto-acoustic simulation relative to other approaches in the literature, and give an overview of our approach.

In Section 3.2, a mathematical model that defines opto-acoustic simulation for a linear array probe is described. The model is represented as a *mathematical operator* that includes the effects of: i) acoustic wave propagation for a 3D volume with constant speed of sound and density; ii) spatial impulse response due to finite transducer aperture on the received signal (e.g. effects of rectangular transducer elements and directionality); and iii) a spatially dependent optical fluence distribution of the delivered light energy. We show how the probe's position and orientation, in a coordinate frame relative to the volume's coordinates, influences the resulting signal. We also demonstrate mathematical properties that are necessary for the following sections.

In Section 3.3, we prove that the mathematical operator developed in Section 3.2 is separable. An exact analytic solution, which is separable, is formulated for when rectangular transducer elements are used. Furthermore, if an exact solution is not required, we also present a far-field approximation that permits additional performance increase.

In Section 3.4, we describe the results of our implementation for fast 3D simulation, and compare the simulated acoustic output to what is obtained with other 3D simulations. In Section 3.5, we discuss the model and analyze its computational complexity. We conclude in Section 3.6. A list of symbols and equations is provided in Table 3.2.1.

3.1.2 Significance

To our best knowledge, our work is the first that involves combining a compositionally-separable time-domain operator for acoustic simulation with an efficient method to include the spatial impulse response from multiplicatively-separable rectangular transducer elements. We also believe that this is the first work to describe a separable operator for 3D acoustic simulation in the rotated frame of a linear array probe, and to recognize that there is computational advantage of doing so during implementation. Also, our proof in Section 3.3, which is based on showing separability using the Dirac delta function, is novel. It illustrates the separability of the 3D acoustic wave Green’s function, and generalizes to a wider class of Green’s function kernels that are separable. Additionally, our opto-acoustic simulation model in Section 3.2 is novel in the sense that the transducer aperture function and the optical energy distribution move in the coordinate reference frame of the linear array relative to the volume’s coordinates, which is applicable for simulating transducer arrays undergoing motion.

3.1.3 Relation to other work

Opto-acoustic imaging is a new modality that has recently been investigated clinically for improved accuracy in breast cancer diagnosis [1]–[7]. The modality is able to visualize breast tumors several centimetres deep within tissue, and may potentially improve distinction between benign and malignant lesions [1]–[4]. The simulation model described in this article was developed by considering the geometry and specifications of a hand-held opto-acoustic probe with a linear transducer array and light delivery unit that would be suitable for clinical imaging.

There are numerous approaches for performing acoustic and opto-acoustic simulations. The approach proposed in our paper is formulated for opto-acoustic simulation in the *time-domain*. For an omni-directional point detector, it is known that opto-acoustic wave propagation can be computed as a convolutional operator in the time-domain, based on a Green’s function solution to the scalar wave equation [5], [6], [8]. Several time-domain based approaches for acoustic simulation that involve rectangular elements [9]–[16] are briefly summarized in this section.

Separable acoustic wave methods have also been studied. The approach of Jakubowicz et al. (1989) [17] showed that seismological migration for 3D acoustic wave fields was separable in the time-domain using cascaded operations. The method involved a *backward* (inversion) operator to *reconstruct* an imaging volume from its measured signals [18]. However, to *simulate* signals from an imaging volume, a *forward* operator is required. By implementing the equations of Jakubowicz et al. [17] in the opposite order, we develop a forward operator that is separable.

Furthermore, we show that efficient computation and separability is still possible when rectangular elements are used, and that the equation can be applied in a rotated coordinate system of the probe.

For approaches of performing simulations in the time-domain, the impulse response for a rectangular element has been well studied [12]–[16], [19], [20]. The exact time-domain impulse response for a rectangular element was described by San Emeterio and Ullate (1992) [16]. For a line source, the exact time-domain impulse response is described by Lasota et al. (1984) [14]. Scarano et al. (1985) [15] proposed an impulse response calculation for rectangular transducer elements that involved a separable aperture function. However, this involved multiplicative separability for rectangular geometry, which is different from our approach that uses separability of convolutional operators by composition. A trapezoidal far-field approximation for the impulse response of rectangular transducers was described by Stepanishen (1971) [13], [21] and Freedman (1971) [22]. McGough (2004) [23] describes rapid calculation of time-harmonic near-field pressures from rectangular elements, which improves numerical performance by removing singularities that arise in integral equations.

Software for acoustic simulation is also available. Field II is a program designed for computing pressure fields from arbitrarily shaped, apodized, and excited ultrasound transducers [11], [12]. The approach subdivides an aperture into multiple rectangular elements. FOCUS is another toolbox, which uses an approach called the fast near-field method to efficiently compute accurate acoustic fields for various geometries [23]–[25]. In Field II, simulation of opto-acoustic signals from a 3D volume can be performed by forming a superposition of weighted impulse responses from a list of absorbers located at different 3D positions. This is less efficient than the proposed approach, which uses volumetric separability to compute output for a linear-array.

In addition to time-domain approaches, separable approaches for acoustic waves models have also been described for the *frequency-domain* [26], [27]. This involves using a pair of two-dimensional cascaded operators (analogous to the cascaded time-domain operators). In each cascaded 2D frequency-domain operation, the space of 2D Fourier data is warped using a non-linear transformation. The frequency-domain computations work best when elements are aligned along a 2D grid, which is preferred for efficient implementation of the multi-dimensional fast Fourier transform operator.

Other frequency-domain methods for computing acoustic signals include pseudo-spectral or “k-space” approaches [28]–[30]. One such simulator, called K-wave [31], is designed to produce opto-acoustic signals from a dense volume with non-homogeneous acoustic properties. For non-homogeneous volumes, k-space methods use temporally discretized steps that compute repeated frequency-domain operations. Each step can be implemented using separable operations; however, general purpose k-space simulation of non-homogeneous volumes cannot exploit the same efficiency that arises in a separable model for the homogeneous case.

For opto-acoustic imaging, the effects of transducer aperture on image reconstruction have previously been studied [32], [33]. In addition, models involving far-field approximations for rectangular elements using a frequency-domain approach have been investigated for use in opto-acoustic reconstruction [34]–[36]. However, these methods do not involve a separable simulation model and are different from our proposed approach.

3.2 OPTO-ACOUSTIC SIMULATION MODEL

In this section, we describe our model for opto-acoustic simulation. Subsequently, in Section 3.3, we will prove that it has an equivalent separable implementation that can be computed efficiently. The model simulates the system-response of a 3D volume of optical absorbers, when illuminated by a pulse of light. It is assumed that the source of light moves in the same coordinate reference frame as a transducer array that records opto-acoustic signals.

In opto-acoustics, signal strength is proportional to a volume’s optical absorption coefficient and to its Grüneisen coefficient. These vary spatially within the 3D volume. When multiplied together, they form a parameter called the *opto-acoustic conversion efficiency*, which is treated as an input to our simulation model. The signal strength is also proportional to the *optical energy distribution*, another system input, which describes the amount of light that reaches each location in the volume.

In the model, it is assumed that the optical energy distribution depends only on *bulk* optical properties of the volume, independent from the volume’s spatially dependent optical absorption coefficient. This approximation makes it possible to rotate and translate the spatial distribution of optical energy, which moves with the position and orientation of the light source. It is also assumed that the acoustic properties of the volume are homogeneous (constant speed of sound, density, etc.).

The output from the simulation includes a set of time-domain acoustic signals corresponding to what would be measured by an array of rectangular transducer elements, positioned in the coordinate frame of the probe relative to the volume.

3.2.1 List of symbols and equations

$\psi(\mathbf{x})$	acoustic source distribution (initial excess pressure)
	$\psi(\mathbf{x}) = \eta(\mathbf{x})\Phi_{A,\mathbf{b}}(\mathbf{x})$
$\eta(\mathbf{x})$	opto-acoustic conversion efficiency
$\Phi(\mathbf{x})$	optical energy distribution
	$\Phi_{A,\mathbf{b}}(\mathbf{x}) = \mathcal{T}_{A,\mathbf{b}}\{\Phi\}(\mathbf{x}) = \Phi(A^T(\mathbf{x} - \mathbf{b}))$
$p(\mathbf{x}, t)$	acoustic pressure
	$p(\mathbf{x}, t) = \mathcal{H}\{\psi\}(\mathbf{x}, t)$
$s(\mathbf{u}, t)$	simulated opto-acoustic signal
	$s(\mathbf{u}, t) = \mathcal{H}_{f,\Phi}^{A,\mathbf{b}}\{\eta\}(\mathbf{u}, t)$
$\mathcal{H}\{\psi\}(\mathbf{x}, t)$	ideal system response operator
$\mathcal{H}_f\{\psi\}(\mathbf{x}, t)$	system response operator for aperture f
$\mathcal{H}^{A,\mathbf{b}}\{\psi\}(\mathbf{u}, t)$	system response operator in probe frame
	$\mathcal{H}_f^{A,\mathbf{b}}\{\psi\}(\mathbf{u}, t) = h_f(\mathbf{u}, t) \underset{\mathbf{u}}{\circledast} \psi(A\mathbf{u} + \mathbf{b})$
$\mathcal{H}_{f,\Phi}^{A,\mathbf{b}}\{\eta\}(\mathbf{u}, t)$	generalized system response operator
	$\mathcal{H}_{f,\Phi}^{A,\mathbf{b}}\{\eta\}(\mathbf{u}, t) = h_f(\mathbf{u}, t) \underset{\mathbf{u}}{\circledast} [\underbrace{\eta(A\mathbf{u} + \mathbf{b})\Phi(\mathbf{u})}_{\psi^{A,\mathbf{b}}(\mathbf{u})}]$
$\mathcal{G}\{\psi\}(\mathbf{x}, t)$	factor of system response operator
	$\mathcal{H}^{A,\mathbf{b}} = \tilde{\mathcal{G}} \circ \mathcal{G}^{A,\mathbf{b}}$
$f_{\mathbf{a}}(\mathbf{x})$	rectangular aperture function
	$f_{\mathbf{a}}(\mathbf{x}) = \text{rect}(\frac{x_1}{a_1}, \frac{x_2}{a_2})\delta(x_3)$
$g(\mathbf{x}, t)$	d'Alembert free-space Green's function
	$g(\mathbf{x}, t) = \frac{1}{4\pi t}\delta(ct - \ \mathbf{x}\)$
$h_f(\mathbf{x}, t)$	pressure impulse response for aperture f
	$h_f(\mathbf{x}, t) = \underbrace{\left[\frac{\partial}{\partial t}g(\mathbf{x}, t)\right]}_{h(\mathbf{x}, t)} \underset{\mathbf{x}}{\circledast} f(\mathbf{x})$
$\bar{h}_f(\mathbf{x}, t)$	modified pressure impulse response for aperture f
	$\bar{h}_f(\mathbf{x}, t) = \underbrace{[h(\mathbf{x}, t)\alpha(\mathbf{x})]}_{\bar{h}(\mathbf{x}, t)} \underset{\mathbf{x}}{\circledast} f(\mathbf{x})$
$\alpha(\mathbf{x})$	obliquity function
$\delta(t)$	Dirac impulse function
$u(t)$	Heaviside step function

$\mathbf{x}$	global volume coordinates in F_0 $\mathbf{x} = (x_1, x_2, x_3)$
$\mathbf{u}$	local coordinates in probe frame F_P $\mathbf{u} = (u_1, u_2, u_3)$
$\hat{\mathbf{e}}_1, \hat{\mathbf{e}}_2, \hat{\mathbf{e}}_3$	standard basis vectors
$\hat{\mathbf{n}}_1, \hat{\mathbf{n}}_2, \hat{\mathbf{n}}_3$	basis vectors for F_P
F_0	base coordinate reference frame
F_P	probe coordinate reference frame
$T_{A,\mathbf{b}}(\mathbf{u})$	affine transform function $T_{A,\mathbf{b}}(\mathbf{u}) = A\mathbf{u} + \mathbf{b}$
$T_{A,\mathbf{b}}^{-1}(\mathbf{x})$	inverse affine transform function $T_{A,\mathbf{b}}^{-1}(\mathbf{x}) = A^T(\mathbf{x} - \mathbf{b})$
$\mathcal{T}_{A,\mathbf{b}}\{\psi\}(\mathbf{x})$	affine transform operator $\mathcal{T}_{A,\mathbf{b}}^{-1}\{\psi\}(\mathbf{u}) = \psi(T_{A,\mathbf{b}}(\mathbf{u})) = \psi^{A,\mathbf{b}}(\mathbf{u})$
A	rotation matrix
$\mathbf{b}$	translation vector
$f \circledast \tilde{f}$	convolution $[f \circledast \tilde{f}](\mathbf{x}) = \int_{\mathbb{R}^3} f(\mathbf{x}') \tilde{f}(\mathbf{x} - \mathbf{x}') d\mathbf{x}'$
$f \circ \mathbf{g}$	composition $[f \circ \mathbf{g}](\mathbf{x}) = f(\mathbf{g}(\mathbf{x}))$ $[\mathcal{S} \circ \tilde{\mathcal{S}}]\{\psi\}(\mathbf{x}) = \mathcal{S}\{\tilde{\mathcal{S}}\{\psi\}\}(\mathbf{x})$
$f \odot \tilde{f}$	pointwise multiplication $[f \odot \tilde{f}](\mathbf{x}) = f(\mathbf{x})\tilde{f}(\mathbf{x})$

3.2.2 Notation and preliminaries

In our notation, vectors and vector functions appear in a bold font (e.g. $\mathbf{x}$, $\mathbf{g}(\mathbf{x})$, ...). Scalars and scalar functions appear in plain font (e.g. f , $g(\mathbf{x})$, k , ...). Spatial position is represented by a vector in Euclidean space. The components of a three-dimensional position vector $\mathbf{x} \in \mathbb{R}^3$ are written x_1, x_2, x_3 . A matrix (e.g. A) is described with uppercase roman letters. The transpose of matrix A is written A^T . Column vectors are written with round brackets, and row vectors use square brackets. Thus, $\mathbf{u} = (u_1, u_2, u_3) = [u_1, u_2, u_3]^T$ and $\mathbf{u}^T = [u_1, u_2, u_3]$. A function is often written without its argument. For example, $\psi(\mathbf{x})$ can be shortened to ψ , when usage is clear from the context. A mathematical operator (e.g. $\mathcal{G}, \mathcal{H}, \mathcal{T}, \dots$), which maps one space of functions to another space of functions, is written with script. When a function ψ is transformed (into a new function)

by an operator $\mathcal{S}$, this is written $\mathcal{S}\{\psi\}$. The affine transform *function* $T_{A,\mathbf{b}}$, which acts on a vector and produces a vector, is written in uppercase; it should not be confused with the affine transform *operator* $\mathcal{T}_{A,\mathbf{b}}$ which acts on a function and produces a function, and is written in script. Also, since the number of letters in the alphabet is limited, a tilde symbol over a letter (e.g. $\tilde{a}, \tilde{\mathcal{G}}, \dots$) is used to indicate a different (and possibly related) variable or operator.

To perform acoustic simulation, operators involving *convolution* and *composition* are used. These are described below.

Composition

The composition of a function $f(\mathbf{x})$ with a function $\mathbf{g}(\mathbf{x})$ is defined as

$$[f \circ \mathbf{g}](\mathbf{x}) \equiv f(\mathbf{g}(\mathbf{x})). \quad (3.1)$$

For composition to be valid, the domain of f must match the result produced by $\mathbf{g}$. For example, if $f: \mathbb{R}^3 \rightarrow \mathbb{R}$ (which means the input of f is a vector in $\mathbb{R}^3$ and its output is a real number), then $\mathbf{g}$ must output a vector in $\mathbb{R}^3$ to match the domain of f .

Composition can also be applied when the function is a matrix. For example, if $A \in \mathbb{R}^{3 \times 3}$, then $[f \circ A](\mathbf{x}) = f(A\mathbf{x})$. Composition with the affine transform function is written $[f \circ T_{A,\mathbf{b}}](\mathbf{x})$, which is equal to $f(T_{A,\mathbf{b}}(\mathbf{x}))$.

Mathematical operators

In this paper, composition is applied to mathematical operators. We refer to the composition of two operators as a *cascade*. For fast acoustic simulation, we are concerned with the cascade $\mathcal{H}\{\psi\}(\mathbf{x}) = [\tilde{\mathcal{G}} \circ \mathcal{G}]\{\psi\}(\mathbf{x})$. That is to say, $\mathcal{H}$ is *compositionally-separable* into $\tilde{\mathcal{G}}$ and $\mathcal{G}$, when applied to any source function ψ . Here, the composition of two operators $\tilde{\mathcal{G}}$ and $\mathcal{G}$ is defined $[\tilde{\mathcal{G}} \circ \mathcal{G}]\{\psi\}(\mathbf{x}) \equiv \tilde{\mathcal{G}}\{\mathcal{G}\{\psi\}\}(\mathbf{x})$.

To be somewhat more precise, a transform operator is a function that transforms one function-space S_1 into another function-space S_2 . One familiar transform operator is the (temporal) Fourier transform $\mathcal{F}: (\mathbb{R} \rightarrow \mathbb{R}) \rightarrow (\mathbb{R} \rightarrow \mathbb{C})$, which converts a real valued function in the time-domain $f(t)$ to a complex-valued function in the frequency domain $\hat{f}(\omega)$, with the relationship $\hat{f}(\omega) = \mathcal{F}\{f\}(\omega)$.

When an operator $\mathcal{S}: S_1 \rightarrow S_2$ is applied to a function $f \in S_1$, this is written as $\mathcal{S}\{f\}(\mathbf{x})$. This means that the function f is transformed by $\mathcal{S}$ from S_1 to S_2 . The result is in the function-space S_2 . The argument $\mathbf{x}$, which is in the domain of S_2 , is applied to the transformed function.

There are two major reasons why operator notation is useful. First, it is similar to linear matrix form (beyond the scope of this paper), which is commonly used in image reconstruction to invert measured data (see [7], [18], [37]–[39]). For example, $\mathcal{H}$ would directly correspond to a discretized system matrix H , which enables solving inverse problems with linear algebra. In a similar manner,

the cascade $\tilde{\mathcal{G}} \circ \mathcal{G}$ corresponds to the matrix multiplication $\tilde{G}G$, where $\tilde{G}$ and G are discretized matrices. This can offer computational advantages [40] when using standard inversion methods. Secondly, for mathematical proofs, our notation succinctly permits manipulation of continuous variables, which are hidden in linear matrix notation. This simplifies mathematical descriptions used in this paper and future work involving image reconstruction [40].

Convolution

The acoustic signal model involves convolution. The convolution of function $f(\mathbf{x})$ with function $g(\mathbf{x})$, in the vector variable $\mathbf{x}$, is defined as

$$[f \circledast g](\mathbf{x}) \equiv \int_{-\infty}^{\infty} f(\mathbf{x}') g(\mathbf{x} - \mathbf{x}') d\mathbf{x}'. \quad (3.2)$$

Here, $d\mathbf{x}'$ stands for $dx'_1 dx'_2 dx'_3$ and implies that the integration is carried out over a triple integral $\int_{-\infty}^{\infty} \int_{-\infty}^{\infty} \int_{-\infty}^{\infty}$ due to the three components of $\mathbf{x}'$. The primed index indicates that the integration is performed over an intermediate variable $\mathbf{x}'$ which is different from (and not to be confused with) the argument variable $\mathbf{x}$. An intermediate vector variable's elements also have primed indices (e.g., x'_1 , x'_2 and x'_3). If convolution is performed in an expression that already has one intermediate variable (e.g. $\mathbf{x}'$), then a double-primed index is used to indicate a second intermediate variable (e.g. $\mathbf{x}''$).

Often, convolution will be performed over a function of several variables, but the integration will only apply to a subset of these variables. This is indicated by placing the name of the applicable integration variable(s) below the convolution symbol. For example, an expression may read $h(\mathbf{x}) = f(\mathbf{x}) \underset{\mathbf{x}}{\circledast} g(\mathbf{x}, t)$. In this case, when a replacement for $\mathbf{x}$ occurs in the left-hand side $h(\mathbf{x})$, then the right-hand side $f(\mathbf{x}) \underset{\mathbf{x}}{\circledast} g(\mathbf{x}, t)$ should be interpreted as in (3.2). An explicit replacement uses lower subscripts on square brackets. For example,

$$\left[f(\mathbf{x}) \underset{\mathbf{x}}{\circledast} g(\mathbf{x}) \right]_{\mathbf{x} = A\mathbf{u} + \mathbf{b}}$$

is equal to

$$\int_{-\infty}^{\infty} f(\mathbf{x}') g(A\mathbf{u} + \mathbf{b} - \mathbf{x}') d\mathbf{x}'.$$

As another shorthand, the expression $f(\mathbf{x}) \underset{x_1, x_2}{\circledast} g(\mathbf{x})$ indicates that the convolution is carried out only over x_1 and x_2 . This avoids having to include a factor of Dirac delta (e.g. $\delta(x_3)$) to cancel the variable that is not integrated over.

3.2.3 Coordinate frames of linear array

In this section we describe the coordinate frames and geometry for the opto-acoustic probe used in our model.

Figure 3.1 shows an opto-acoustic probe with linear array in a rotated coordinate frame. The coordinate frame of the probe is F_P . The probe (and thus its coordinate frame) is located at position $\mathbf{b}$, relative to the base coordinate system F_0 . The advantage of this setup is that the 3D volume of acoustic sources can be maintained in F_0 , which facilitates computation. Light is delivered from F_P , so the optical energy distribution remains stationary relative to the probe, but is translated and rotated relative to the volume.

The vector $\mathbf{x} \in \mathbb{R}^3$ is used to describe a position in the global frame F_0 , and the vector $\mathbf{u} \in \mathbb{R}^3$ describes a position in the local frame of the probe F_P .

The probe orientation is represented by direction vectors $\hat{\mathbf{n}}_1$, $\hat{\mathbf{n}}_2$, and $\hat{\mathbf{n}}_3$ that point along the axes of the probe. In a linear array, the elements of the array are arranged on a line pointing along the $\hat{\mathbf{n}}_1$ axis. Therefore, in frame F_0 , the line of elements is given by the equation

$$\mathbf{x} = \hat{\mathbf{n}}_1 u_1 + \mathbf{b}, \quad (3.3)$$

where u_1 is a positive or negative distance from $\mathbf{b}$ in the $\hat{\mathbf{n}}_1$ direction. In frame F_P , a position on the line of transducer elements corresponds to $\mathbf{u} = (u_1, 0, 0)$. The k -th element of the array is located at $u_1 = (k - 1)\Delta_{u_1} + u_0$, where the element spacing is Δ_{u_1} , and the first element's position corresponds to u_0 .

We consider a rigid coordinate transform from F_P to F_0 using an affine transformation. Let $A \in \mathbb{R}^{3 \times 3}$ be a rotation matrix, and $\mathbf{b} \in \mathbb{R}^3$ be a spatial displacement vector. The function $T_{A,\mathbf{b}}(\mathbf{u})$ applies the rotation A to $\mathbf{u}$, followed by a translation of $\mathbf{b}$. Thus, conversion between the local coordinates $\mathbf{u}$ of the probe and global coordinates $\mathbf{x}$ of the volume can be performed by

$$\mathbf{x} = T_{A,\mathbf{b}}(\mathbf{u}) = A\mathbf{u} + \mathbf{b} \quad (3.4a)$$

$$\mathbf{u} = T_{A,\mathbf{b}}^{-1}(\mathbf{x}) = A^T(\mathbf{x} - \mathbf{b}). \quad (3.4b)$$

The rotation matrix A for converting orientation from F_P to F_0 is given by

$$A = \begin{bmatrix} a_{11} & a_{12} & a_{13} \\ a_{21} & a_{22} & a_{23} \\ a_{31} & a_{32} & a_{33} \end{bmatrix} = \begin{bmatrix} \uparrow & \uparrow & \uparrow \\ \hat{\mathbf{n}}_1 & \hat{\mathbf{n}}_2 & \hat{\mathbf{n}}_3 \\ \downarrow & \downarrow & \downarrow \end{bmatrix}. \quad (3.5)$$

The columns of the rotation matrix correspond to the direction vectors $\hat{\mathbf{n}}_1$, $\hat{\mathbf{n}}_2$, and $\hat{\mathbf{n}}_3$ for the probe orientation. The direction vectors form an orthonormal coordinate system, and are related by $\hat{\mathbf{n}}_1 \cdot \hat{\mathbf{n}}_2 = \hat{\mathbf{n}}_2 \cdot \hat{\mathbf{n}}_3 = \hat{\mathbf{n}}_3 \cdot \hat{\mathbf{n}}_1 = 0$ and $\hat{\mathbf{n}}_3 = \hat{\mathbf{n}}_1 \times \hat{\mathbf{n}}_2$. Since the columns are orthogonal unit vectors, the matrix A is orthogonal; therefore, its inverse A^{-1} is equal to its transpose A^T , which is a property of rotation matrices. The translation $\mathbf{b}$ is the position of the probe in F_0 , as shown in Figure 3.1.

At any position $\mathbf{u}$ in the local coordinate frame of the probe, a position $\mathbf{x}$ in volume coordinates can be found from Equation (3.4a). To convert to local coordinates from volume coordinates, the inverse transform of Equation (3.4b) is used.

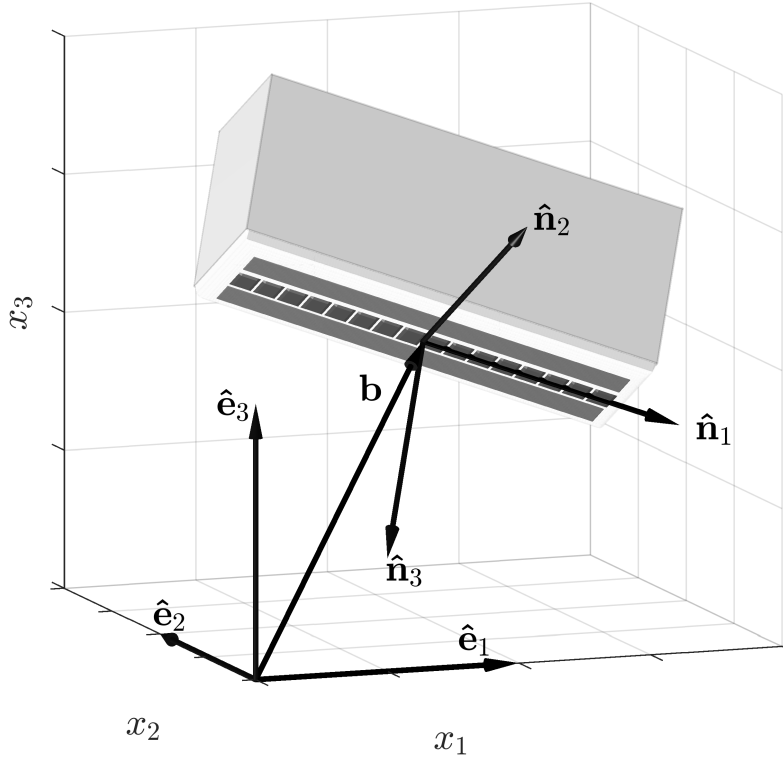


Figure 3.1: Geometry of an opto-acoustic probe in rotated and translated coordinate system. A linear array of 16 transducer elements (small dark rectangles on the probe face) is shown along the $\hat{n}_1$ axis. Two rectangular optical source apertures (long dark rectangles on the probe face) are shown adjacent to the array, which illustrate how light is delivered to the volume in a typical scenario. The basis vectors for the probe's local coordinate frame F_P , are $\hat{n}_1$, $\hat{n}_2$, and $\hat{n}_3$. For the global coordinate frame F_0 , the standard basis vectors $\hat{e}_1$, $\hat{e}_2$, and $\hat{e}_3$ are used. The probe is translated from the origin by $\mathbf{b}$, and rotated by the rotation matrix $A = [\hat{n}_1 \ \hat{n}_2 \ \hat{n}_3]$.

There is a special situation for a linear-array. When $\mathbf{u} = (u_1, 0, 0)$, which means it is constrained to the $\hat{n}_1$ axis, then $T_{A,\mathbf{b}}([u_1, 0, 0]^T)$ reduces to Equation (3.3), which is the equation of a line in F_0 . Also, applying $T_{A,\mathbf{b}}$ to the plane $\mathbf{u} = (u_1, 0, u_3)$ will produce a plane in F_0 corresponding to the *imaging plane* cross section of the volume. The imaging plane is what would be seen on the display of a 2D imaging device when the probe is in position over an imaging volume. When $\mathbf{u} = (0, u_2, u_3)$, this corresponds to a plane perpendicular to the imaging plane in F_0 .

The affine transform function $T_{A,\mathbf{b}}$, acts on a vector and generates a vector. This is different from the affine transform operator $\mathcal{T}_{A,\mathbf{b}}$, which acts on a function and produces a rotated and translated version of that function. In certain proofs we rely on one or the other, so we are careful to point out the distinction.

The affine transform operator (and its inverse), are defined by

$$\mathcal{T}_{A,\mathbf{b}}\{\psi\}(\mathbf{x}) = [\psi \circ T_{A,\mathbf{b}}^{-1}](\mathbf{x}) = \psi(A^T(\mathbf{x} - \mathbf{b})), \quad (3.6a)$$

$$\mathcal{T}_{A,\mathbf{b}}^{-1}\{\psi\}(\mathbf{u}) = [\psi \circ T_{A,\mathbf{b}}](\mathbf{u}) = \psi(A\mathbf{u} + \mathbf{b}). \quad (3.6b)$$

If a function $\psi(\mathbf{x})$, which describes a spatial distribution, is shifted *in one direction*, this corresponds its argument $\mathbf{x}$, which is a coordinate vector, being shifted *in the opposite direction*. Accordingly, $\mathcal{T}$ is defined by composition with the inverse of T . In this sense, T and $\mathcal{T}$ behave oppositely.

In our model, the probe orientation is specified with a rotation matrix. Arbitrary rotation matrices can be formed by applying a sequence of Euler matrices corresponding to *roll*, *pitch* and *yaw* angles. To generate an arbitrary rotation matrix A , we use the convention

$$A = R_1(\theta_1)R_2(\theta_2)R_3(\theta_3), \quad (3.7)$$

where the matrices for roll, pitch and yaw are

$$R_1(\theta_1) = \begin{bmatrix} 1 & 0 & 0 \\ 0 & \cos(\theta_1) & -\sin(\theta_1) \\ 0 & \sin(\theta_1) & \cos(\theta_1) \end{bmatrix}, \quad (\text{roll}) \quad (3.8a)$$

$$R_2(\theta_2) = \begin{bmatrix} \cos(\theta_2) & 0 & \sin(\theta_2) \\ 0 & 1 & 0 \\ -\sin(\theta_2) & 0 & \cos(\theta_2) \end{bmatrix}, \quad (\text{pitch}) \quad (3.8b)$$

$$R_3(\theta_3) = \begin{bmatrix} \cos(\theta_3) & -\sin(\theta_3) & 0 \\ \sin(\theta_3) & \cos(\theta_3) & 0 \\ 0 & 0 & 1 \end{bmatrix}. \quad (\text{yaw}) \quad (3.8c)$$

In subsequent sections, we convert between coordinates in equations involving both convolution and composition. The following formula for changing variables is useful when working with an impulse response $h(\mathbf{u})$ defined in a local coordinate system, and a spatial distribution $\psi(\mathbf{x})$ defined in a global coordinate system. The coordinate $\mathbf{x}$ is related to the coordinate $\mathbf{u}$ by $\mathbf{x} = T_{A,\mathbf{b}}(\mathbf{u})$. For convolution of the functions $h(\mathbf{u})$ and $\psi(\mathbf{x})$, a change of coordinates corresponds to the relationship

$$\left[(h \circ T_{A,\mathbf{b}}^{-1}) \circledast \psi \right](\mathbf{x}) = \frac{1}{|\det A|} \left[h \circledast (\psi \circ T_{A,\mathbf{b}}) \right](\mathbf{u}).$$

This can be seen by writing out the convolutional expression $h(\mathbf{u}) \circledast \psi(\mathbf{x})$ in expanded form with $\mathbf{u} = T_{A,\mathbf{b}}^{-1}(\mathbf{x})$. The differential element $d\mathbf{u}$ is scaled by the determinant of A because $d\mathbf{u} = d(A^{-1}(\mathbf{x} - \mathbf{b})) = |\det A|^{-1} d\mathbf{x}$. For a rotation matrix, since $\det A$ always equals 1, the relationship we are interested in simplifies to

$$\left[\mathcal{T}_{A,\mathbf{b}}\{h\} \circledast \psi \right](\mathbf{x}) = \left[h \circledast \mathcal{T}_{A,\mathbf{b}}^{-1}\{\psi\} \right](\mathbf{u}), \quad (3.9)$$

where $\mathbf{x} = T_{A,\mathbf{b}}(\mathbf{u}) = A\mathbf{u} + \mathbf{b}$.

Also, if no rotation is performed, and the coordinates are in the same frame, this will reduce to the (more well known) translation property of convolution, which is

$$\left[\mathcal{T}_{I,\mathbf{b}}\{h\} \otimes \psi \right](\mathbf{x}) = \left[h \otimes \mathcal{T}_{I,\mathbf{b}}\{\psi\} \right](\mathbf{x}),$$

where I is the identity matrix, so $\mathcal{T}_{I,\mathbf{b}}$ is a pure translation. The interpretation is that a translation can go with either function in the convolution, when compared in the same coordinate frame.

3.2.4 Opto-acoustic signals

The opto-acoustic signal generation model is now described. We develop a generalized *system response operator*, that includes: i) transducer aperture, ii) light distribution, iii) probe position, and iv) probe orientation. In our notation, the operator is written $\mathcal{H}_{f,\Phi}^{A,\mathbf{b}}\{\eta\}(\mathbf{u}, t)$. The most simple way to think of this is as a “function” that outputs a time-domain signal (in the variable t), for a transducer centered at position $\mathbf{u}$ in the probe’s coordinate frame. Here, A and $\mathbf{b}$ specify the probe orientation and position. The function f specifies the aperture geometry, and Φ specifies optical energy distribution. The 3D volume is described by η .

The system response operator is developed in three parts. First, we model a system response operator $\mathcal{H}_f$ in a local coordinate frame, and generalize this to transformed coordinates with A and $\mathbf{b}$.

Next, we describe opto-acoustic wave propagation in more detail and explain the physics for the transducer impulse response. This will provide context for our derivations in the following sections.

Finally, we build on this to include light distribution Φ , emitted from the coordinate frame of a probe.

Spatio-temporal impulse response

Heating a medium with an optical pulse at time $t = 0$ causes an *initial acoustic source distribution* $\psi(\mathbf{x})$, which propagates as an acoustic wave. In our notation, the *simulated opto-acoustic signal* $s(\mathbf{x}, t)$, measured by an ideal transducer with aperture f , at time t , and position $\mathbf{x}$, is written

$$s(\mathbf{x}, t) = \mathcal{H}_f\{\psi\}(\mathbf{x}, t). \quad (3.10)$$

The operator $\mathcal{H}_f$ performs convolution of $\psi(\mathbf{x})$ with $h_f(\mathbf{x}, t)$. Thus,

$$\mathcal{H}_f\{\psi\}(\mathbf{x}, t) = h_f(\mathbf{x}, t) \otimes_{\mathbf{x}} \psi(\mathbf{x}). \quad (3.11)$$

The function $h_f(\mathbf{x}, t)$ is the *pressure impulse response for aperture f* . It is defined by convolution of $f(x)$ with $h(\mathbf{x}, t)$, according to

$$h_f(\mathbf{x}, t) = h(\mathbf{x}, t) \otimes_{\mathbf{x}} f(\mathbf{x}). \quad (3.12)$$

Here, $h(\mathbf{x}, t)$ is the *free-space pressure impulse response* given by

$$h(\mathbf{x}, t) = \frac{\partial}{\partial t} \frac{\delta(c_0 t - \|\mathbf{x}\|)}{4\pi t}, \quad (3.13)$$

which is described in the next subsection. The speed of sound c_0 is assumed to be constant, and δ is the Dirac impulse function.

When f is an aperture function, it is defined

$$f(\mathbf{x}) = \begin{cases} 1, & \text{if } -\mathbf{x} \text{ is on transducer's surface,} \\ 0, & \text{otherwise.} \end{cases} \quad (3.14)$$

A weighted aperture could also be used (where the value on the transducer surface depends on $\mathbf{x}$), but this is not implemented in this work.

The aperture function describes the geometry of the transducer elements. A rectangular transducer has a length a_1 and width a_2 . The *rectangular transducer aperture function*, where $\mathbf{a} = (a_1, a_2)$, is defined as

$$f_{\mathbf{a}}(\mathbf{x}) = \text{rect}\left(\frac{x_1}{a_1}, \frac{x_2}{a_2}\right) \delta(x_3), \quad (3.15)$$

where

$$\text{rect}(x_1, x_2) = \begin{cases} 1, & |x_1| \leq \frac{1}{2} \text{ and } |x_2| \leq \frac{1}{2}, \\ 0, & \text{otherwise.} \end{cases}$$

When the transducer is an *ideal point detector*, the aperture is $f_{\delta}(\mathbf{x}) = \delta(\mathbf{x})$. In this case, the system response operator can be written $\mathcal{H}\{\psi\}(\mathbf{x}, t)$ (with no subscripts), since (3.12) yields $h_{f_{\delta}}(\mathbf{x}, t) = h(\mathbf{x}, t) \underset{\mathbf{x}}{\circledast} \delta(\mathbf{x}) = h(\mathbf{x}, t)$.

To provide transducer responses with a directional component, we define a *modified system response operator* (written using a bar symbol)

$$\overline{\mathcal{H}}_f\{\psi\}(\mathbf{x}, t) = \overline{h}_f(\mathbf{x}, t) \underset{\mathbf{x}}{\circledast} \psi(\mathbf{x}), \quad (3.16)$$

where

$$\overline{h}_f(\mathbf{x}, t) = \underbrace{[h(\mathbf{x}, t)\alpha(\mathbf{x})]}_{\overline{h}(\mathbf{x}, t)} \underset{\mathbf{x}}{\circledast} f(\mathbf{x}). \quad (3.17)$$

The *modified pressure impulse response* $\overline{h}(\mathbf{x}, t)$ is spatially weighted by $\alpha(\mathbf{x})$. The function $\alpha(\mathbf{x})$, which is called the *obliquity factor* [9], [10], [13], [19], describes the directional response to waves arriving from different angles. It is defined by

$$\alpha(\mathbf{x}) = \frac{\mathbf{x} \cdot \hat{\mathbf{n}}}{\|\mathbf{x}\|}, \quad (3.18)$$

where $\hat{\mathbf{n}}$ is the outward normal to the transducer at $\mathbf{x}$. In our notation, the bar symbol (over the system operator and impulse responses) indicates that the obliquity factor $\alpha(\mathbf{x})$ is included. When it is present, a transducer measures the unbalanced component of force, normal to the transducer's surface. Otherwise, the transducer measures the excess acoustic pressure. The choice depends on the type of transducer that is being modeled. For a soft-baffle transducer, which is constrained to receive axial forces, the obliquity factor is present; for a rigid-baffle transducer, which receives omni-directional forces, it is not present.

In the sections below we will show a proof for both types of transducer, with and without obliquity factor. When either case is relevant, this will be made clear from the context.

It is convenient to include position and orientation in the notation of the system response operator. This is because when dealing with rotation, both the aperture and probe must be rotated simultaneously, which follows from (3.9). (If only $\mathbf{u}$ is rotated, then $\mathcal{H}_f$ is not applicable because its aperture f is non-rotated). Accordingly, the definition of $\mathcal{H}_f^{A,b}$ is

$$\begin{aligned}\mathcal{H}_f^{A,b}\{\psi\}(\mathbf{u}, t) &= \mathcal{H}_f\{\mathcal{T}_{A,b}^{-1}\{\psi\}\}(\mathbf{u}, t) \\ &= [\mathcal{H}_f \circ \mathcal{T}_{A,b}^{-1}]\{\psi\}(\mathbf{u}, t) \\ &= \mathcal{H}_f\{\psi \circ T_{A,b}\}(\mathbf{u}, t) \\ &= \mathcal{H}_f\{\psi^{A,b}\}(\mathbf{u}, t),\end{aligned}\tag{3.19}$$

where we have defined the oppositely rotated and translated volume as

$$\psi^{A,b}(\mathbf{u}) = \mathcal{T}_{A,b}^{-1}\{\psi\}(\mathbf{u}) = \psi(T_{A,b}(\mathbf{u})).\tag{3.20}$$

After the simulated system response has been computed, a purely temporal *electro-mechanical impulse response* $h_{\text{em}}(t)$ can be applied to it, if desired, to model the system bandwidth. Post-processing with temporal convolution is written

$$h_{\text{em}}(t) \otimes_t \mathcal{H}_f^{A,b}\{\psi\}(\mathbf{x}, t).\tag{3.21}$$

Equation (3.21) decouples the temporal response from the geometry of the transducer element's aperture. The remainder of this paper assumes an ideal electro-mechanical impulse response, where $h_{\text{em}}(t)$ is equal to $\delta(t)$, which leaves $\mathcal{H}_f^{A,b}$ unaltered and does not affect computation. This assumption is used because opto-acoustic signals have broadband frequency content, which is due to using nearly instantaneous optical pulses, as described in the next section.

Opto-acoustic wave propagation

The opto-acoustic physics relevant to our model is now described. First, the pressure impulse response function $h(\mathbf{x}, t)$ in (3.13) is derived. This corresponds to solving the acoustic wave equation with an instantaneous heating source term (see Chapter 7 of Morse and Ingard (1968) [8];

Oraevsky (2014) [5]; and Xu et al. (2006) [6]). Next, a derivation is provided for (3.16) that incorporates transducer directionality into the model. Some of the details of this section will be used in demonstrating the separable cascade described in Section 3.3.

In opto-acoustics, a pulse of light rapidly heats optical absorbers in a volume. Thermal expansion due to the heating pulse creates a spatial distribution of omni-directional sources that radiate acoustic waves [8]. The acoustic waves propagate according to the acoustic wave equation for pressure $p(\mathbf{x}, t)$, given by

$$\left(\frac{\partial^2}{\partial t^2} - c_0^2 \nabla^2\right)p(\mathbf{x}, t) = \psi(\mathbf{x}) \frac{\partial}{\partial t} q(t). \quad (3.22)$$

Here, the source term $\psi(\mathbf{x}) \frac{\partial}{\partial t} q(t)$ is present only for the short duration of the pulse. We have arranged the source term as the product of a temporal factor $(\partial/\partial t)q(t)$ and a spatial factor $\psi(\mathbf{x})$, which simplifies the derivation below. The function $q(t)$ is the temporal pulse shape, i.e., the time-domain waveform of the laser. It is assumed that $q(t)$ is sufficiently short so thermal and stress conformation occurs (i.e., thermal conduction and wave propagation in the medium are negligible for the duration of the pulse.) This maximizes energy converted to acoustic waves. We also assume $q(t) > 0$ for all t , and $\int_{-\infty}^{+\infty} q(t) dt = 1$, so $q(t)$ does not impact the total amount of energy delivered, just its shape. For an instantaneous pulse, $q(t)$ is equal to $\delta(t)$, which is an assumption used in most of this paper for simplification.

The spatial distribution $\psi(\mathbf{x})$ is an instantaneous acoustic source term known as the *initial excess pressure*, which results from optical heating as described in the next section (see equation (3.31)).

At an arbitrary position $\mathbf{x}$ and time t , the wave equation from (3.22) has a solution for pressure $p(\mathbf{x}, t)$ of

$$p(\mathbf{x}, t) = g(\mathbf{x}, t) \underset{\mathbf{x}, t}{\otimes} \psi(\mathbf{x}) \frac{\partial}{\partial t} q(t), \quad (3.23)$$

where

$$g(\mathbf{x}, t) = \frac{\delta(c_0 t - \|\mathbf{x}\|)}{4\pi t}. \quad (3.24)$$

The function $g(\mathbf{x}, t)$ is known as the causal Green's function solution to the three-dimensional d'Alembert wave equation in free-space (a.k.a. the *delayed free-space Green's function*)*, which permits Equation (3.23) to be written in convolutional form.

* The Green's function $g(\mathbf{x}, t)$ can appear in several equivalent forms. This is because: i) the impulse occurs with $\|\mathbf{x}\| = ct$; and ii) the scaling property of the Dirac impulse function obeys the identity $\delta(t - x/c) \equiv c\delta(ct - x)$. Therefore, $g(\mathbf{x}, t) \equiv \frac{1}{4\pi\|\mathbf{x}\|}\delta\left(t - \frac{\|\mathbf{x}\|}{c}\right) \equiv \frac{1}{4\pi ct}\delta\left(t - \frac{\|\mathbf{x}\|}{c}\right) \equiv \frac{1}{4\pi t}\delta(ct - \|\mathbf{x}\|) \equiv \frac{c}{4\pi\|\mathbf{x}\|}\delta(ct - \|\mathbf{x}\|)$. In addition, iii) some authors divide the wave equation (Equation (3.22)) on both sides by c^2 , in which case $g(\mathbf{x}, t)$ would appear with an additional factor of c^{-2} to conserve units. We are concerned with the pressure impulse response $h(\mathbf{x}, t)$, which is proportional to the time-derivative of $g(\mathbf{x}, t)$. In cases where this time-derivative is evaluated analytically, it is convenient to use a form of $g(\mathbf{x}, t)$ where t is in its denominator (instead of $\|\mathbf{x}\|$), to make it apparent that the dependency of $\|\mathbf{x}\|$ on t requires using the product rule. However, for evaluating a spatial gradient of $g(\mathbf{x}, t)$, this is most apparent in forms with $\|\mathbf{x}\|$ in the denominator.

Since the source term of (3.23) is multiplicatively separable in $\mathbf{x}$ and t , it can also be written

$$p(\mathbf{x}, t) = g(\mathbf{x}, t) \otimes_t \frac{\partial q(t)}{\partial t} \otimes_x \psi(\mathbf{x}).$$

Due to the commutative-derivative property of convolution (the derivative can be performed on either convolutional factor), the $\frac{\partial}{\partial t}$ can be moved from q to g . Therefore, $p(\mathbf{x}, t)$ is equal to

$$\frac{\partial g(\mathbf{x}, t)}{\partial t} \otimes_t q(t) \otimes_x \psi(\mathbf{x}).$$

By defining the free-space pressure impulse response as

$$h(\mathbf{x}, t) = \frac{\partial g(\mathbf{x}, t)}{\partial t}, \quad (3.25)$$

this becomes

$$p(\mathbf{x}, t) = h(\mathbf{x}, t) \otimes_t q(t) \otimes_x \psi(\mathbf{x}), \quad (3.26)$$

which demonstrates that the pressure resulting from an arbitrary pulse shape is a temporal convolution with $q(t)$. For an instantaneous pulse, when $q(t) = \delta(t)$, this simplifies to

$$p(\mathbf{x}, t) = h(\mathbf{x}, t) \otimes_x \psi(\mathbf{x}). \quad (3.27)$$

When a transducer centered at position $\mathbf{x}$ measures pressure by integrating over the aperture $f(\mathbf{x})$, the resulting signal is

$$h(\mathbf{x}, t) \otimes_x f(\mathbf{x}) \otimes_x \psi(\mathbf{x}),$$

which matches the form of Equation (3.11) that defines $\mathcal{H}_f$. To include an arbitrary pulse shape $q(t)$ in the resulting time-domain signal, a temporal convolution with $q(t)$ can be performed after the measured signal has been computed (similar to Equation (3.21)). Since this can be applied in post-processing, and grouped with h_{em} of Equation (3.21), we focus only on the case where an instantaneous pulse shape is used. Therefore, $q(t)$ is not part of our core model, although the effect can be incorporated if necessary. Rapid or instantaneous pulses generate opto-acoustic signals with broadband frequency content. Increasing the pulse width causes a low-pass filtering effect in accordance with the frequency response of $q(t)$.

The physics for $\overline{\mathcal{H}}_f$, when the obliquity factor $\alpha(\mathbf{x})$ is present, is now described. If $\mathbf{x}$ represents position on the transducer surface, the net component of force density resulting from the pressure gradient, acting on the transducer in its inward normal direction $\hat{\mathbf{n}}$, is

$$-\nabla p(\mathbf{x}, t) \cdot \hat{\mathbf{n}}.$$

The total force acting on the transducer surface S is thus

$$\int_S \nabla p(\mathbf{x}, t) \cdot \hat{\mathbf{n}} \, dS.$$

This can be written as a spatial convolution with an aperture function $f(\mathbf{x})$. Furthermore, by using a temporal convolution, it can be applied to an electro-mechanical impulse response for pressure $h_{\text{em}}^{\text{p}}(t)$, which describes how the transducer responds to a pressure input. This yields the transducer output signal as

$$h_{\text{em}}^{\text{p}}(t) \otimes_t (\nabla p(\mathbf{x}, t) \cdot \hat{\mathbf{n}}) \otimes_{\mathbf{x}} f(\mathbf{x}). \quad (3.28a)$$

Equation (3.28a) can also be written in terms of the *velocity potential* $\phi(\mathbf{x}, t)$, which is related to pressure by $p(\mathbf{x}, t) = \varrho_0 \frac{\partial}{\partial t} \phi(\mathbf{x}, t)$, where ϱ_0 is mass-density. In this case, the electromechanical impulse response for velocity $h_{\text{em}}^{\text{v}}(t)$ can be used instead of $h_{\text{em}}^{\text{p}}(t)$. These are related by $h_{\text{em}}^{\text{p}}(t) = \varrho_0 \frac{\partial}{\partial t} h_{\text{em}}^{\text{v}}(t)$ (i.e., the step response for measuring pressure is the impulse response for measuring velocity.) Thus, equation (3.28a) can be written equivalently as

$$h_{\text{em}}^{\text{v}}(t) \otimes_t \left(\frac{1}{\varrho_0} \nabla \phi(\mathbf{x}, t) \cdot \hat{\mathbf{n}} \right) \otimes_{\mathbf{x}} f(\mathbf{x}). \quad (3.28b)$$

By taking the gradient of Equation (3.27), the pressure gradient is equal to[†]

$$\nabla p(\mathbf{x}, t) = \nabla h(\mathbf{x}, t) \otimes_{\mathbf{x}} \psi(\mathbf{x}) = h(\mathbf{x}, t) \otimes_{\mathbf{x}} \nabla \psi(\mathbf{x}).$$

Using this with the definition of velocity potential, and from Equation (3.25), we can write the gradient of the velocity potential in terms of the free-space Green's function $g(\mathbf{x}, t)$. Thus

$$\frac{1}{\varrho_0} \nabla \phi(\mathbf{x}, t) = \nabla g(\mathbf{x}, t) \otimes_{\mathbf{x}} \psi(\mathbf{x}). \quad (3.29)$$

From Equation (3.24) and (3.25), and since the impulse occurs at $\|\mathbf{x}\| = c_0 t$, the spatial gradient of $g(\mathbf{x}, t)$ is

$$\begin{aligned} \nabla g(\mathbf{x}, t) &= \sum_i \frac{\partial g(\mathbf{x}, t)}{\partial x_i} \hat{\mathbf{e}}_i \\ &= \sum_i \frac{\partial g(\mathbf{x}, t)}{\partial t} \frac{\partial t}{\partial x_i} \hat{\mathbf{e}}_i \\ &= \frac{1}{c_0} \frac{\partial g(\mathbf{x}, t)}{\partial t} \sum_i \frac{\partial \|\mathbf{x}\|}{\partial x_i} \hat{\mathbf{e}}_i \\ &= \frac{1}{c_0} h(\mathbf{x}, t) \frac{\mathbf{x}}{\|\mathbf{x}\|}. \end{aligned}$$

Therefore

$$\nabla g(\mathbf{x}, t) \cdot \hat{\mathbf{n}} = \frac{h(\mathbf{x}, t)}{c_0} \frac{\mathbf{x} \cdot \hat{\mathbf{n}}}{\|\mathbf{x}\|} = \frac{h(\mathbf{x}, t)}{c_0} \alpha(\mathbf{x}).$$

By applying the dot product of $\hat{\mathbf{n}}$ to both sides of (3.29), this gives

$$\frac{1}{\varrho_0} \nabla \phi(\mathbf{x}, t) \cdot \hat{\mathbf{n}} = \frac{\bar{h}(\mathbf{x}, t)}{c_0} \otimes_{\mathbf{x}} \psi(\mathbf{x}).$$

[†] The gradient can be grouped with either convolutional factor, due to the commutative-derivative property of convolution $\nabla[f(x) \otimes g(x)] = \nabla f(x) \otimes g(x) = f(x) \otimes \nabla g(x)$

By substitution into equation (3.28b), and by ignoring the electromechanical impulse response of the transducer (and its gain), the overall transducer output signal is proportional to

$$\overbrace{\left[\underbrace{h(\mathbf{x}, t) \alpha(\mathbf{x})}_{\bar{h}(\mathbf{x}, t)} \right]}^{\bar{h}_f(\mathbf{x}, t)} \underset{\mathbf{x}}{\otimes} f(\mathbf{x}) \underset{\mathbf{x}}{\otimes} \psi(\mathbf{x}).$$

This matches the form of Equation (3.16), where $\bar{\mathcal{H}}_f$ is defined.

By omitting the obliquity factor $\alpha(\mathbf{x})$, this reduces to the form of equation (3.11), where the transducer is modeled by integrating pressure over an aperture.

Optical energy delivery

In our model, the optical energy distribution $\Phi(\mathbf{u})$ remains stationary relative to the local coordinate frame F_P of the probe. The optical energy that gets delivered in the global coordinate frame F_0 corresponds to rotating and translating $\Phi(\mathbf{u})$ according to the position and orientation of the probe. As shown in Figure 3.1, the probe is positioned at $\mathbf{b}$ and rotated by A . The relationship between local coordinate $\mathbf{u}$ and global coordinate $\mathbf{x}$ is

$$\mathbf{u} = T_{A, \mathbf{b}}^{-1}(\mathbf{x}) = A^T(\mathbf{x} - \mathbf{b}).$$

Therefore, the light distribution $\Phi(\mathbf{u})$ in frame F_0 corresponds to

$$\begin{aligned} \Phi_{A, \mathbf{b}}(\mathbf{x}) &= [\Phi(\mathbf{u})]_{\mathbf{u}=T_{A, \mathbf{b}}^{-1}(\mathbf{x})} \\ &= \Phi(T_{A, \mathbf{b}}^{-1}(\mathbf{x})) = \mathcal{T}_{A, \mathbf{b}}\{\Phi\}(\mathbf{x}). \end{aligned} \quad (3.30)$$

Here, the rotated and translated optical energy distribution that is delivered to the global frame is called $\Phi_{A, \mathbf{b}}(\mathbf{x})$. Notice that applying the affine transformation operator $\mathcal{T}_{A, \mathbf{b}}$ to Φ , which forwardly rotates the distribution by A and translates it by $\mathbf{b}$, is equivalent to composition of the inverse transformation function $T_{A, \mathbf{b}}^{-1}$ with its input.

In opto-acoustics, the initial excess pressure distribution $\psi(\mathbf{x})$ is the product of the opto-acoustic conversion efficiency $\eta(\mathbf{x})$ times the optical energy distribution $\Phi(\mathbf{u})$. Thus,

$$\psi(\mathbf{x}) = \eta(\mathbf{x}) \Phi_{A, \mathbf{b}}(\mathbf{x}). \quad (3.31)$$

The opto-acoustic conversion efficiency η describes the amount of light per unit energy that is converted into acoustic pressure at each location in the medium. It is equal to the optical absorption coefficient μ_a times the Grüneisen parameter Γ , both which may vary spatially in the medium. Therefore,

$$\eta = \Gamma \mu_a.$$

The coefficient μ_a determines how much optical energy is absorbed and converted to heat. The pressure increase due to thermal expansion per unit energy gained is determined by Γ . It is equal to

$$\Gamma = \frac{\beta}{\kappa \varrho_0 c_V} = \frac{\beta c_0^2}{c_P},$$

which depends on the speed of sound c_0 , specific heats c_P and c_V , mass density ϱ_0 , compressibility κ , and thermal expansion β coefficients.

To facilitate including light distribution in our model, we extend the definition of the system response operator $\mathcal{H}$. Recall from Equation (3.19), the affine transformed system response for ψ is

$$\begin{aligned} \mathcal{H}_f^{A,b}\{\psi\}(\mathbf{u}, t) &= \mathcal{H}_f\{\mathcal{T}_{A,b}^{-1}\{\psi\}\}(\mathbf{u}, t) \\ &= \mathcal{H}_f\{\psi^{A,b}\}(\mathbf{u}, t), \end{aligned}$$

where $\psi^{A,b}(\mathbf{u}) = \mathcal{T}_{A,b}^{-1}\{\psi\}(\mathbf{u})$. The operator applies an inverse affine transform operator to ψ , or equivalently stated, it operates directly on $\psi^{A,b}$. From Equation (3.31), in frame F_0 , the acoustic source distribution ψ is given by the product

$$\begin{aligned} \psi(\mathbf{x}) &= \eta(\mathbf{x}) \Phi_{A,b}(\mathbf{x}) \\ &= [\eta \odot \Phi_{A,b}](\mathbf{x}). \end{aligned}$$

The symbol “ $\odot$ ” represents multiplication, which is applied pointwise on the two functions[‡]. Thus,

$$\psi = \eta \odot \Phi_{A,b}.$$

Therefore, by applying $\mathcal{T}_{A,b}^{-1}$ to both sides, the acoustic source distribution in the local frame F_P , denoted $\psi^{A,b}$, is

$$\begin{aligned} \psi^{A,b}(\mathbf{u}) &= \mathcal{T}_{A,b}^{-1}\{\eta \odot \Phi_{A,b}\}(\mathbf{u}) \\ &= \mathcal{T}_{A,b}^{-1}\{\eta \odot \Phi_{A,b}\}(\mathbf{u}) \\ &= \eta(T_{A,b}(\mathbf{u})) \Phi_{A,b}(T_{A,b}(\mathbf{u})) \\ &= \eta^{A,b}(\mathbf{u}) \Phi(\mathbf{u}) \\ &= [\eta^{A,b} \odot \Phi](\mathbf{u}), \end{aligned}$$

where $\eta^{A,b}(\mathbf{u}) = \mathcal{T}_{A,b}^{-1}\{\eta\}(\mathbf{u})$. In summary, the relationship for the acoustic source distribution in either frame is

$$\psi(\mathbf{x}) = [\eta \odot \Phi_{A,b}](\mathbf{x}), \quad (3.32a)$$

$$\psi^{A,b}(\mathbf{u}) = [\eta^{A,b} \odot \Phi](\mathbf{u}). \quad (3.32b)$$

[‡] For discretized functions, the $\odot$ operation corresponds to a Hadamard product. Support for this is directly built in to the syntax of some high-level languages, including Matlab.

Here, because the optical energy distribution can be represented in the local frame $\Phi(\mathbf{u})$, it is independent of the position and orientation of the probe. Therefore, to include optical energy distribution in the model, the system response operator must perform a pointwise multiplication by Φ , which remains the same even if the probe moves.

Accordingly, the system response operator that includes the optical energy distribution is defined as

$$\begin{aligned}\mathcal{H}_{f,\Phi}^{A,\mathbf{b}}\{\eta\} &= \mathcal{H}_f^{A,\mathbf{b}}\{\psi\} \\ &= \mathcal{H}_f\{\mathcal{T}_{A,\mathbf{b}}^{-1}\{\eta\} \odot \Phi\} \\ &= \mathcal{H}_f\{\eta^{A,\mathbf{b}} \odot \Phi\}.\end{aligned}\tag{3.33}$$

Here, the optical energy distribution Φ appears in the subscript of $\mathcal{H}_{f,\Phi}^{A,\mathbf{b}}\{\eta\}$ to indicate that it is multiplied with the conversion efficiency η after being rotated. This notation is convenient because when the probe is translated and rotated, the light distribution stays fixed relative to the probe.

Computing the optical energy distribution $\Phi(\mathbf{u})$ is now briefly described. In our model, we assume that regardless of the probe orientation and position, $\Phi(\mathbf{u})$ will not change. This would be applicable in two situations: a) when the bulk optical properties of the tissue medium are assumed to be homogeneous; and, b) the bulk optical properties of the tissue are layered and the probe moves along the surface, so that by translational symmetry, the motion doesn't alter the optical fluence distribution relative to the probe. In both cases, it is assumed that $\Phi(\mathbf{u})$ is not affected by local changes in optical absorption $\mu_a(\mathbf{x})$.

The optical energy distribution is governed by the radiation transport equation [41]–[47]. The number of photons that reach positions in the medium depend on its local optical properties, which change with optical wavelength and the configuration of the optical source aperture. Light distributions can be solved in several ways, including diffusion approximations [41]–[44], finite-element models [45], or Monte Carlo based methods [46], [47].

When delivering light through an optical source aperture, the optical energy distribution $\Phi(\mathbf{u})$ can be computed in two steps. First, an intermediate distribution $\tilde{\Phi}(\mathbf{u})$ for a pencil-beam (point aperture) is produced. Then, spatial convolution of $\tilde{\Phi}(\mathbf{u})$ with an optical aperture function yields $\Phi(\mathbf{u})$. For a rectangular optical source aperture with dimensions $\mathbf{a} = (a_1, a_2)$, centered at the origin, the energy distribution is

$$\Phi(\mathbf{u}) = \tilde{\Phi}(\mathbf{u}) \underset{u_1, u_2}{\otimes} \text{rect}\left(\frac{u_1}{a_1}, \frac{u_2}{a_2}\right).\tag{3.34}$$

A simple method to compute $\tilde{\Phi}(\mathbf{u})$ involves an empirically derived analytical model for a half-space of optically homogeneous tissue [41]. The optical energy distribution from a point source is modeled in terms of a material's *effective optical attenuation* μ_{eff} by

$$\tilde{\Phi}(\mathbf{u}) = \frac{\mu_{\text{eff}}^2}{4\pi} \left(\frac{\exp(-\mu_{\text{eff}} \|\mathbf{u} - (0, 0, z_0)\|)}{\|\mathbf{u} - (0, 0, z_0)\|} - \frac{\exp(-\mu_{\text{eff}} \|\mathbf{u} + (0, 0, z_0 + 2z_b)\|)}{\|\mathbf{u} + (0, 0, z_0 + 2z_b)\|} \right),$$

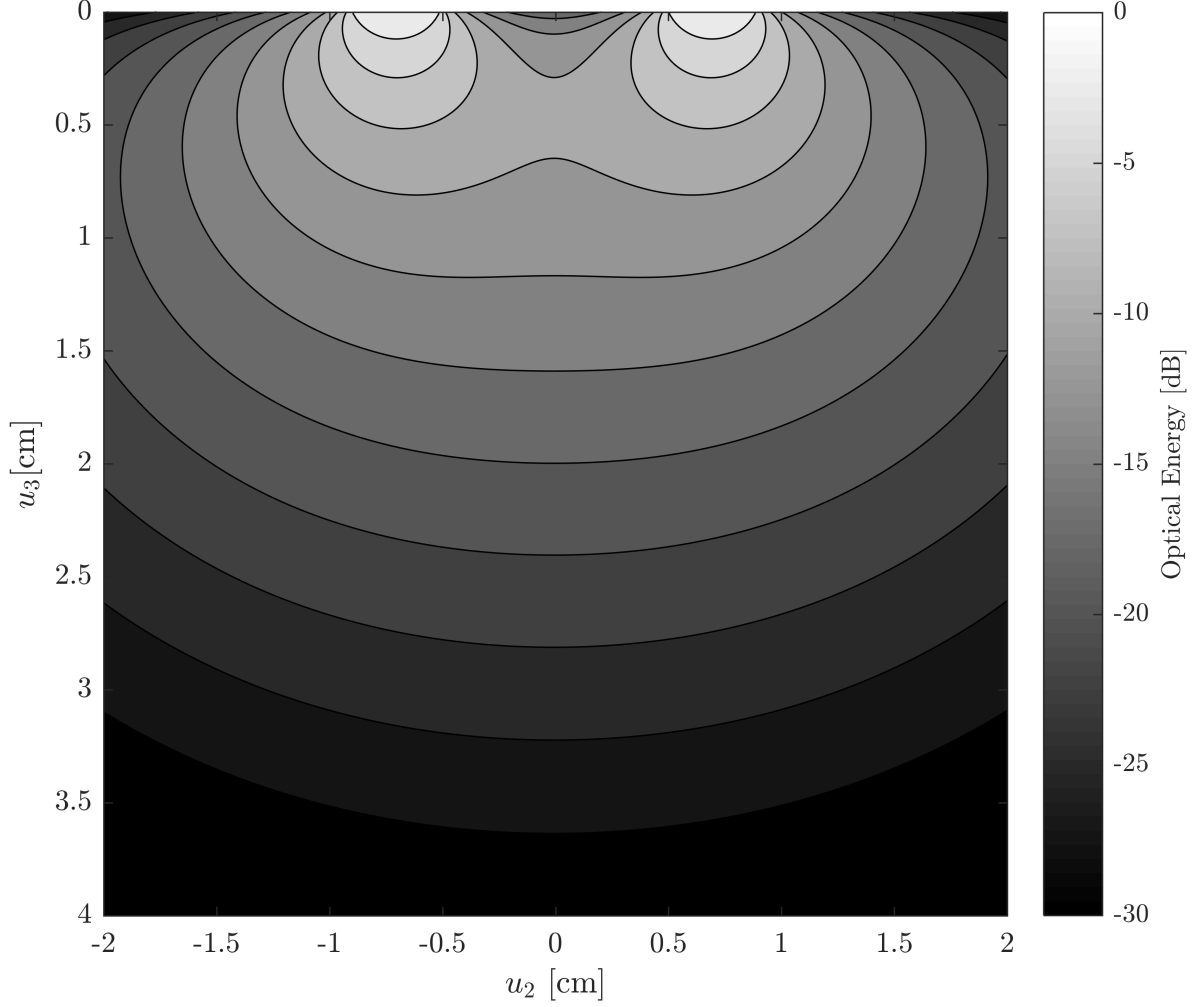


Figure 3.2: Cross section of a typical optical energy distribution $\Phi(\mathbf{u})$ for probe in contact with tissue. The 2D cross-section represents the u_2 - u_3 -plane of the transducer at $u_1 = 0$. The delivered optical energy is highest near each of the optical source apertures located at the tissue surface. The imaging plane corresponds to a vertical line at $u_2 = 0$. Tissue is modeled with effective optical attenuation $\mu_{\text{eff}} = 1.8\text{cm}^{-1}$ for optical wavelength $\lambda = 757\text{nm}$. As the probe moves, $\Phi(\mathbf{u})$ remains fixed relative to the probe coordinate system $\mathbf{u}$.

where z_0 is the mean-free path length and z_b is a negative image source distance (see Farrell et al. (1992) [41]). Further enhancements to include directed photons are described by Zemp (2013) [42].

In Figure 3.2, the optical energy distribution is shown when applied to a probe with two rectangular optical source apertures using spatial convolution of Equation (3.34) with (3.35). This matches the geometry of Figure 3.1. The delivered optical energy is highest near each of the optical source apertures, which are located at the tissue surface. As the probe moves, $\Phi(\mathbf{u})$ remains fixed relative to the probe coordinate system $\mathbf{u}$. Therefore $\Phi(\mathbf{u})$ only needs to be computed once (per optical wavelength), and can then be cached. This permits more elaborate methods of computing a fluence distribution to be used in place of Equations (3.34) and (3.35).

3.3 SEPARABLE CASCADE

We demonstrate that the system response operator $\mathcal{H}_{f,\Phi}^{A,b}$ described in Section 3.2 can be computed by a separable cascade. Using a separable operator permits an order-of-magnitude reduction in processing time compared to a non-separable operator.

First, in Section 3.3.1, we show that the system response operator $\mathcal{H}^{A,b}$ can be separated into operator factors, in an arbitrary coordinate frame.

In Section 3.3.2, we show that when a multiplicatively separable transducer aperture function $f(\mathbf{x}) = f_1(x_1)f_2(x_2)\delta(x_3)$ is used, then the multiplicative factors f_1 and f_2 can be grouped with the factors of the system response.

In Section 3.3.3, we show that when the obliquity function is used to include directionality, the modified operator $\overline{\mathcal{H}}_{f,\Phi}^{A,b}$ is still separable.

In Section 3.3.4, we demonstrate that when a rectangular transducer aperture is used, a far-field approximation can be used to make the computation even more efficient.

To simplify the expressions in this section, we set speed of sound $c_0 = 1$ and mass-density $\rho_0 = 1$.

3.3.1 Separability of the system response for acoustic pressure

In the local probe frame F_P , the system response for acoustic pressure, from Equation (3.19), is

$$p(\mathbf{u}, t) = \mathcal{H}\{\psi^{A,b}\}(\mathbf{u}, t) = h(\mathbf{u}, t) \underset{\mathbf{u}}{\circledast} \psi^{A,b}(\mathbf{u}),$$

where $\psi^{A,b} = \mathcal{T}_{A,b}^{-1}\{\psi\}$ is the (oppositely) rotated and translated acoustic source distribution for ψ .

To show that this is separable in an arbitrary coordinate frame, in the following proposition we split $\mathcal{H}^{A,b}$ into the factors $\mathcal{G}^{A,b}$ and $\tilde{\mathcal{G}}$. The first factored operator $\mathcal{G}^{A,b}$ acts on two-dimensional slices, to span the entire three-dimensional volume (see Figure 3.3a). The second factored operator $\tilde{\mathcal{G}}$ also acts in two-dimensional slices, but these are rotated, so they only span a two-dimensional subspace of the previous output, because all of the transducer elements in the array are co-linear (see Figure 3.3b).

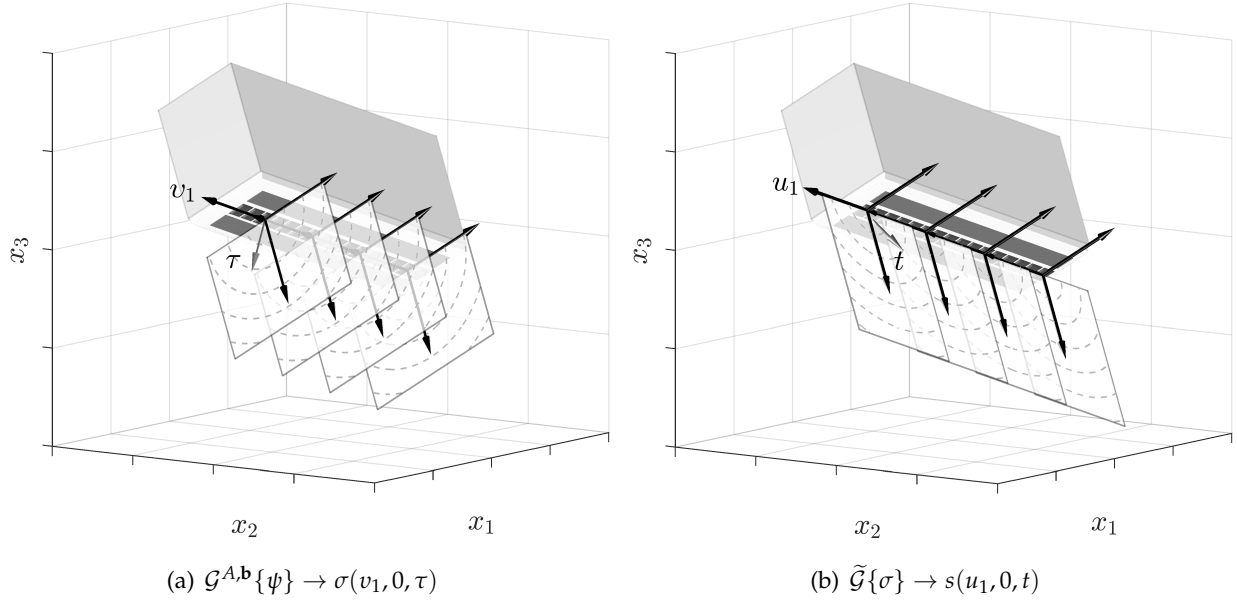


Figure 3.3: Cascaded separable operators for linear array applied to a spatial source distribution $\psi(\mathbf{x})$. (a) At each displacement v_1 along the line of transducer elements $\mathbf{x} = A[v_1, 0, 0]^T + \mathbf{b}$, the operator $\mathcal{G}^{A,b}\{\psi\}$ produces $\sigma(v_1, 0, \tau)$, an intermediate result, by performing integration along an arc of radius τ , in a plane normal to the line of transducer elements. The integration paths span the three-dimensional space ψ (in the planes as shown) by varying v_1 and τ . (b) At each displacement u_1 in the local coordinate system, the operator $\mathcal{G}^{[R_3^{90}, 0]}\{\sigma\}$ produces $s(u_1, 0, t)$ by performing integration along an arc of radius t in a plane rotated by 90° . The integration paths span a two-dimensional subspace of σ (shown as the imaging plane), coinciding with the domain $(v_1, 0, \tau)$ of the previous operation.

To keep the dimensions equal for each operator factor, and show that both factors involve rotated versions of the same operator, we set $u_3 = 0$ in the definition below. Thus, $\mathcal{H}^{A,b}$ outputs a function of three arguments u_1 , u_2 and t . However, in a linear array, only u_1 and t are relevant, since transducer positions are on the line $u_3 = u_2 = 0$.

Proposition 3.1 (Separability of acoustic pressure impulse response in transformed coordinates).
Let the operator $\mathcal{H}^{A,b}$ be defined by

$$\mathcal{H}^{A,b}\{\psi\}(u_1, u_2, t) = \left[h(\mathbf{u}, t) \underset{\mathbf{u}}{\otimes} \psi^{A,b}(\mathbf{u}) \right]_{u_3=0},$$

where $h(\mathbf{u}, t) = \frac{1}{4\pi} \frac{\partial}{\partial t} \frac{\delta(t - \|\mathbf{u}\|)}{t}$ and $\psi^{A,b} = \mathcal{T}_{A,b}^{-1}\{\psi\}$. Then it can be computed using a separable cascade according to

$$\mathcal{H}^{A,b} = \tilde{\mathcal{G}} \circ \mathcal{G}^{A,b},$$

where

$$\mathcal{G}^{A,b}\{\psi\}(u_1, u_2, t) = t \int_0^{2\pi} \psi^{A,b} \left(\begin{bmatrix} u_1 \\ u_2 - t \cos \theta \\ -t \sin \theta \end{bmatrix} \right) d\theta,$$

and

$$\tilde{\mathcal{G}}\{\psi\}(u_1, u_2, t) = \frac{1}{4\pi} \frac{\partial}{\partial t} \left(\frac{1}{t} \mathcal{G}^{R_3(90^\circ), 0} \{\psi\}(u_2, -u_1, t) \right).$$

Proof. The proof for Proposition 3.1 is demonstrated in Appendix 3.A.1. $\square$

3.3.2 Separability with transducer aperture function

In this section we show that the operator $\mathcal{H}_f^{A, \mathbf{b}}$ retains its compositional separability when a multiplicatively separable aperture function $f(\mathbf{u}) = f_1(u_1)f_2(u_2)\delta(u_3)$ is used. This becomes useful for computing the operator efficiently when using a rectangular aperture function $f_{\mathbf{a}}(\mathbf{x}) = \text{rect}\left(\frac{x_1}{a_1}, \frac{x_2}{a_2}\right)\delta(x_3)$.

Here, we are interested developing the factors $\mathcal{G}_{f_i}$ so that the separable cascade has the form

$$\mathcal{H}_f^{A, \mathbf{b}} = \tilde{\mathcal{G}}_{f_1} \circ \mathcal{G}_{f_2}^{A, \mathbf{b}}.$$

The subscripts f_1 and f_2 indicate that a factored 1D aperture function is paired with each separable operator factor.

Proposition 3.2 (Compositional separability for multiplicatively separable aperture). *If an aperture function $f(\mathbf{u})$ can be written as a multiplicatively separable function $f(\mathbf{u}) = f_1(u_1)f_2(u_2)\delta(u_3)$, then the operator $\mathcal{H}_f^{A, \mathbf{b}}$ can be computed by a separable cascade, according to*

$$\mathcal{H}_f^{A, \mathbf{b}} = \tilde{\mathcal{G}}_{f_1} \circ \mathcal{G}_{f_2}^{A, \mathbf{b}},$$

where

$$\tilde{\mathcal{G}}_{f_1}(u_1, u_2, t) = \tilde{\mathcal{G}}(u_1, u_2, t) \underset{u_1}{\otimes} f_1(u_1),$$

and

$$\mathcal{G}_{f_2}^{A, \mathbf{b}}(u_1, u_2, t) = \mathcal{G}^{A, \mathbf{b}}(u_1, u_2, t) \underset{u_2}{\otimes} f_2(u_2).$$

Here, the operators $\tilde{\mathcal{G}}$ and $\mathcal{G}^{A, \mathbf{b}}$ are defined as in Proposition 3.1.

Proof. The proof for Proposition 3.2 is provided in Appendix 3.A.2. $\square$

3.3.3 Separability with obliquity factor

In this section we demonstrate that operator $\overline{\mathcal{H}}_f^{A, \mathbf{b}}$ is separable when the obliquity factor $\alpha(\mathbf{x}) = \frac{\mathbf{x} \cdot \hat{\mathbf{n}}}{\|\mathbf{x}\|}$ is included to obtain a more realistic pressure impulse response. From equations (3.16) and (3.19), the modified operator in the local coordinate $\mathbf{u}$ is

$$\overline{\mathcal{H}}_f^{A, \mathbf{b}}\{\psi\}(\mathbf{u}, t) = [h(\mathbf{u}, t)\alpha(\mathbf{u})] \underset{\mathbf{u}}{\otimes} f(\mathbf{u}) \underset{\mathbf{u}}{\otimes} \psi^{A, \mathbf{b}}(\mathbf{u}),$$

where

$$\psi^{A,\mathbf{b}}(\mathbf{u}) = \mathcal{T}_{A,\mathbf{b}}^{-1}\{\psi\}(\mathbf{u}).$$

We prove that its computation only requires adding simple pre- and post-multiplications to the separable operator $\mathcal{H}$.

Proposition 3.3 (Separability of system response with obliquity factor). *The operator $\overline{\mathcal{H}}_f^{A,\mathbf{b}}$ can be computed by separable cascade according to*

$$\overline{\mathcal{H}}_f^{A,\mathbf{b}}\{\psi\}(u_1, u_2, t) = \frac{1}{t} \mathcal{H}\{\tilde{\psi}^{A,\mathbf{b}}\}(u_1, u_2, t) \underset{u_1, u_2}{\circledast} f(u_1, u_2),$$

where

$$\tilde{\psi}^{A,\mathbf{b}}(\mathbf{u}) = u_3 \psi^{A,\mathbf{b}}(\mathbf{u}).$$

Proof. The proof for Proposition 3.3 is provided in Appendix 3.A.3. □

3.3.4 Far-field approximation to improve performance

In this section, a far-field approximation to improve performance for computing $\mathcal{G}_{f_i}$ is demonstrated for rectangular apertures. This avoids computing a spatial convolution with the aperture function $f_a(\mathbf{x})$ on the 3D volume $\psi(\mathbf{x})$. It also avoids using 1D spatial convolutions as described in Proposition 3.2. The resulting computation involves integration along a path consisting of two positive circular arcs, two negative circular arcs and connecting lines, as shown in Figure 3.4b. Following this, efficient time-domain filtering operations (integration and multiplication) are performed, which results in the desired signals. The far-field approximation becomes more accurate when $\mathbf{x} \gg a$. Thus, the approach is applicable when extreme accuracy is not required in the near-field. However, even when used in the near-field, the far-field approximation may provide more realism compared to modeling an ideal point aperture.

Proposition 3.4 (Far-field approximation to improve performance). *Let a separable factor of the system response be defined by*

$$\mathcal{G}\{\psi\}(u_1, u_2, t) = \left[\psi(\mathbf{u}) \underset{\mathbf{u}}{\circledast} \delta(u_1) \delta(t - \|\mathbf{u}\|) \right]_{u_3=0},$$

and its convolution with a rectangular pulse of width a be defined by

$$\mathcal{G}_a\{\psi\}(u_1, u_2, t) = \text{rect}\left(\frac{u_2}{a}\right) \underset{u_2}{\circledast} \mathcal{G}\{\psi\}(u_1, u_2, t).$$

Then, $\mathcal{G}_a$ can be computed as

$$\mathcal{G}_a\{\psi\}(u_1, u_2, t) = t \int_0^t dt \frac{\partial}{\partial t} \left(\frac{1}{t} \mathcal{G}_a\{\psi\}(u_1, u_2, t) \right),$$

where $\frac{\partial}{\partial t} \left(\frac{1}{t} \mathcal{G}_a \right)$ is approximated by integrating $\psi(z, x, y)$ over six contours according to

$$\begin{aligned}
\frac{\partial}{\partial t} \left(\frac{1}{t} \mathcal{G}_a \{ \psi \} (u_1, u_2, t) \right) \approx & \\
& + t \int_{\frac{\pi}{2}}^{\frac{3\pi}{2}} \psi \left(\begin{bmatrix} u_1 \\ (u_2 + a) - t \cos \theta \\ t \sin \theta \end{bmatrix} \right) \frac{1}{\gamma(t, \theta)} d\theta \\
& - t \int_{-\frac{\pi}{2}}^{\frac{\pi}{2}} \psi \left(\begin{bmatrix} u_1 \\ (u_2 + a) - t \cos \theta \\ t \sin \theta \end{bmatrix} \right) \frac{1}{\gamma(t, \theta)} d\theta \\
& - t \int_{\frac{\pi}{2}}^{\frac{3\pi}{2}} \psi \left(\begin{bmatrix} u_1 \\ (u_2 - a) - t \cos \theta \\ t \sin \theta \end{bmatrix} \right) \frac{1}{\gamma(t, \theta)} d\theta \\
& + t \int_{-\frac{\pi}{2}}^{\frac{\pi}{2}} \psi \left(\begin{bmatrix} u_1 \\ (u_2 - a) - t \cos \theta \\ t \sin \theta \end{bmatrix} \right) \frac{1}{\gamma(t, \theta)} d\theta \\
& + \int_{-\frac{a}{2}}^{\frac{a}{2}} \psi \left(\begin{bmatrix} u_1 \\ u_2 - x \\ t \end{bmatrix} \right) dx \\
& + \int_{-\frac{a}{2}}^{\frac{a}{2}} \psi \left(\begin{bmatrix} u_1 \\ u_2 - x \\ -t \end{bmatrix} \right) dx,
\end{aligned}$$

where

$$\gamma(t, \theta) = \max \left(\frac{a}{2}, t |\cos \theta| \right).$$

Here, the 2D system response factor operator $\mathcal{G}\{\psi\}(u_1, u_2, t)$ has a 3D input domain ψ and produces a 3D scalar output that is parametrized by (u_1, u_2, t) . It is considered 2D because at a fixed value of u_1 , the span of its integration is on a 2D plane, as shown in Figure 3.3a. This is also the case for Figure 3.3b, but where u_2 is the fixed parameter (along the line of the array elements, u_2 equals 0).

Proof. The proof for Proposition 3.4 is provided in Appendix 3.A.4. $\square$

Note that an additional assumption can be made if there is zero signal that arrives from behind the transducer, which is typically desired in practice. Instead of six contours, there would only be five (since one of the connecting lines is on the opposite side of the transducer). In addition, each arc would cover an angle of $\frac{\pi}{2}$ rather than π , since integration does not need to be performed in the half-space behind the transducer.

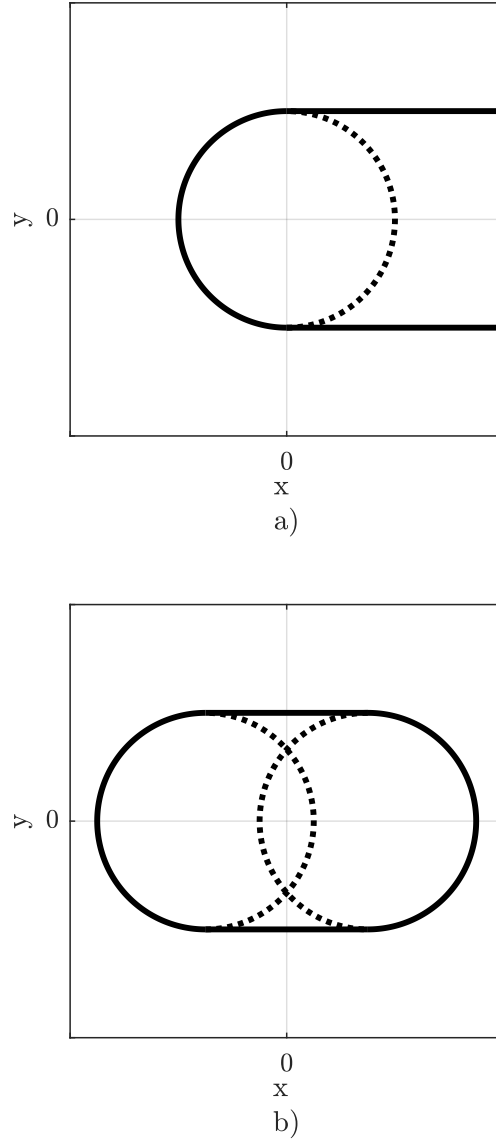


Figure 3.4: Spatial impulse responses in the $z = 0$ plane. Solid line represents positive wavefront and dotted line represents negative wavefront. a) The ray impulse response $\zeta(x, y, t)$ at time t is $\zeta(x, y, t) = \frac{1}{2}\delta(t \pm y)u(x) - \delta(t - \sqrt{x^2 + y^2})\text{sign}(x)$, which traces out the path shown. b) The impulse response $h(x, y, t)$ at time t from a line segment of width a . This is formed by superposition of responses from two rays, with $h(x, y, t) = \zeta(x + a/2, y, t) - \zeta(x - a/2, y, t)$.

3.4 RESULTS AND IMPLEMENTATION

A model for opto-acoustic simulation using a separable mathematical operator was implemented as described in Section 3.2 and Section 3.3. To achieve high performance for computing $\mathcal{H}_{f,\Phi}^{A,b}$, a custom GPU (Graphics Processing Unit) kernel was developed to implement the separable operator factor $\mathcal{G}_f^{A,b}$ and its adjoint. The GPU kernel was developed using CUDA. Testing involved using a GeForce GTX Titan X graphics processor, which has 3072 parallel cores and 12GB of graphics memory. The GPU kernel was configured to run from within a Matlab software environment. A user interface was developed to adjust the position and orientation of a linear-array probe relative to a volume of acoustic sources, as illustrated in Figure 3.5. Controls were implemented to adjust roll, pitch and yaw, as well as the geometry parameters for the transducer elements. Simulation from a volume consisting of $512 \times 512 \times 512$ voxels was capable of achieving real-time performance for generating time-domain data with output of 256 transducer channels and 1024 samples per channel. In Matlab, the display was updated at a rate of 5 frames per second, which could be increased by reducing the size of the volume. Computation times for various grid sizes are provided in Table 3.1.

In Figure 3.5, the configuration of a 128-channel linear-array and its imaging plane are shown, relative to a volume consisting of seven spherical opto-acoustic sources. The linear-array output is shown in Figure 3.6, generated from simulation based on Prop 3.1 using the ideal point detector to produce 512 time-domain samples. A pictorial representation of the time-domain data, called a *sinogram*, is shown along with time-domain traces from selected channels of the dataset. In our implementation, to avoid aliasing, the temporal sampling rate f_s is set by default to the critical rate f_c . This is determined based on the desired number of samples n_s and the voxel spacing $\Delta x = L_z/n_z$, according to $f_c = \frac{c_0}{\Delta x}$, where L_z and n_z are length and number of voxels along the z-axis, and c_0 is speed of sound.

To demonstrate the accuracy of the model, a volume consisting of a single point absorber was compared to time-domain impulse responses that were simulated using the acoustic software package Field II [11], [12]. In Figure 3.7, the impulse response output for rectangular aperture using the exact separable method according to Proposition 3.2 is shown. The output corresponds to signal produced by the point absorber, which is modeled as point source at a fixed location that is detected by different transducers in the linear-array. The output from the exact separable method closely matches that of Field II, except for differences that are attributed to a low-pass filtering effect due to the voxel spacing used in the simulation, where a linear interpolation kernel is used. The effect reduces the intensity of the peak impulses in time-domain, and the magnitude of the transfer-function in frequency-domain is reduced at high frequencies, as shown. This occurs because Field II is capable of simulating a point source with a high bandwidth. However, our method is voxel-based. A voxel is a finite sized object which depends on the 3D grid sizing of the volume. Tri-linear interpolation filters smooth the impulse response from each voxel, and this

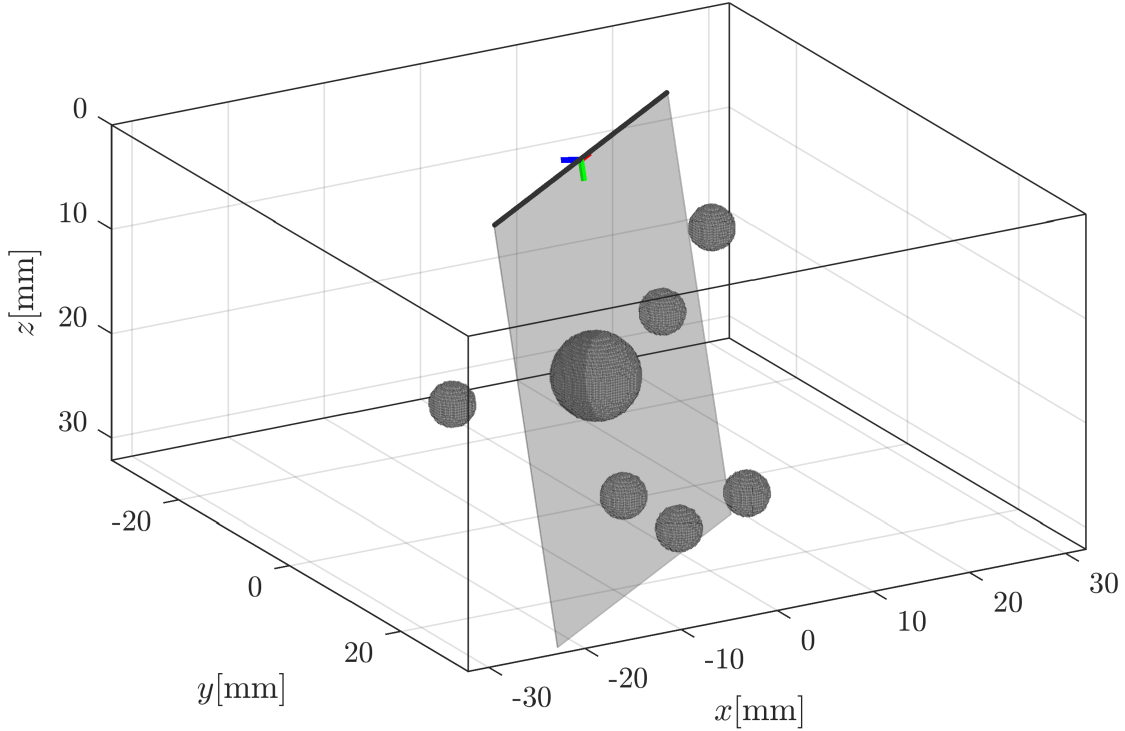


Figure 3.5: A 3D volume consisting of several spherical opto-acoustic sources of equal intensity. Position of linear array is indicated by a dark line, shown adjacent to imaging plane cross-section. The volume consists of $256 \times 256 \times 128$ voxels, corresponding to dimensions of $64 \times 64 \times 32$ mm.

causes the observed time-domain low-pass effects. However, the grid can be made arbitrarily fine to alleviate this if the number of voxels is increased, or if the volume dimensions are decreased, which can increase memory usage and/or processing time.

In Figure 3.8, the far-field approximation of Proposition 3.4 was used to generate time-domain output. As expected, it is seen that the far-field approximation does not match the Field II output as closely as for the exact approach of Figure 3.7, although there is still a close correspondence. Also, the timing of the rising and falling edges do match closely. Some features of the waveform shape and the approximate area of under the curves are also captured by the approximation. Use of Proposition 3.4 is suitable when a balance between speed and accuracy is required.

In Figure 3.9, simulation with transducer aperture for an ideal point detector is compared to a 4mm-wide line aperture. A digital phantom consisting of two spherical absorbers was generated as shown in Figure 3.10. This phantom was designed to produce out-of-plane artifact in 2D imaging, which results because one sphere generates acoustic interference when the probe is positioned over the other. The spheres have 10mm diameter, a 16mm center depth, and homogeneous optical absorption coefficient of 1 arb.u. The background was assumed to have negligible absorption. The simulated volume had $256 \times 256 \times 128$ voxels, with grid spacing $\Delta x = 0.5$ mm/voxel. Both transducers modeled cosine directivity using the obliquity factor $\alpha(\mathbf{x})$ according to Proposition 3.3, with ideal electro-mechanical impulse response $h_{\text{em}}(t) = \delta(t)$. The spheres produced “N-shaped”

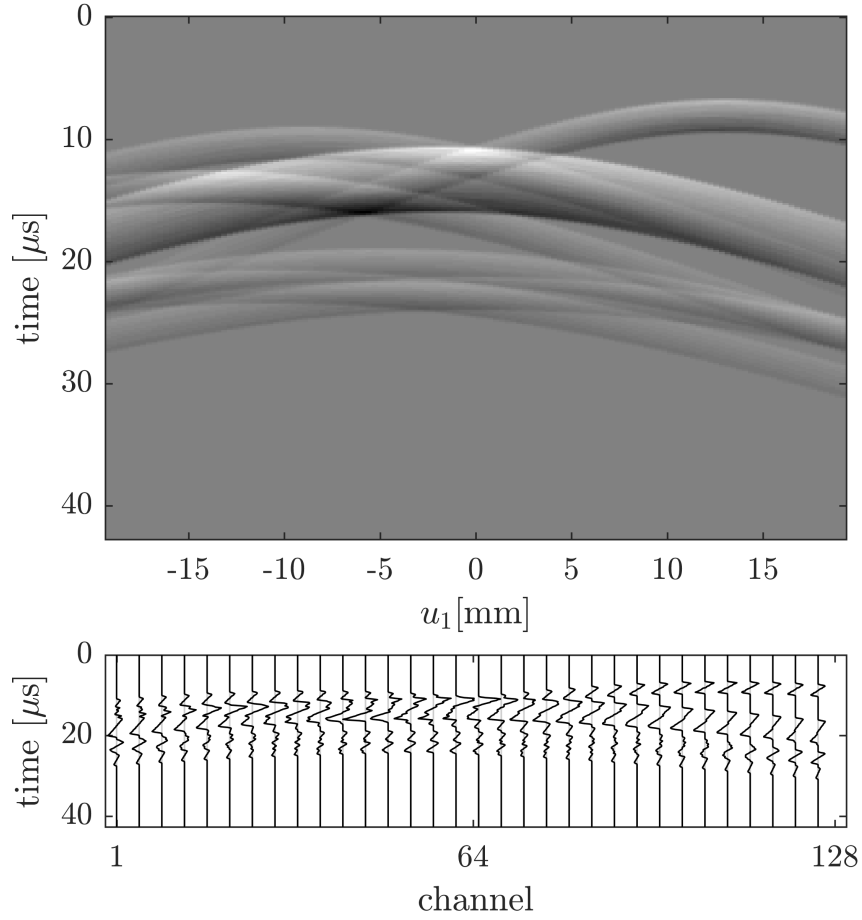


Figure 3.6: Simulated time-domain signals generated by opto-acoustic sources as configured in Figure 3.5. (top) Sinogram image showing signal intensity. (bottom) Line plot of the signals for selected channels.

waveforms, which was expected. The wide aperture provides increased directionality, which filters out more signal from the out-of-plane sphere, as shown. Further analysis regarding image reconstruction using the dataset of Figure 3.9 is described in our follow-up paper [40].

3.5 DISCUSSION

As mentioned earlier, it may be less efficient to perform spatial convolutions per the separable method of Proposition 3.2, compared to the separable far-field approximation described in Proposition 3.4. This is because in modern programmable computing architectures, the time required to perform arithmetic operations may be dwarfed by the time required for non-cached memory accesses. This means that copying data from one memory bank to another, which requires little or no arithmetic processing, could take nearly as much processing time as a well implemented but extensive mathematical transformation performed on the same data. For computing a convolution with an aperture function, by including a step of forming a temporary intermediate output, or

by having to fetch additional samples from memory, this can be less efficient than grouping a few extra arithmetic operations within the separable cascade. When speed is more critical than accuracy, a far-field approximation such as the one proposed in Proposition 3.4 can improve throughput. However, if higher accuracy is required, then Proposition 3.2 may be preferred over Proposition 3.4. Nevertheless, even when Proposition 3.2 is used, the computation is still an order-of-magnitude reduced compared to a non-separable implementation.

An analysis of the computational complexity for each approach is summarized in Table 3.2. In Table 3.3, a description of the variables used in this analysis is provided. In the 3D grid, the number of voxels in the x , y and z directions are n_x , n_y and n_z . The total number of voxels is $N = n_x \times n_y \times n_z$. The number of frames that are acquired by the linear array is m_y (we assume that there is one frame acquired per laser pulse). Since each frame uses all transducer elements in the linear-array to record data, m_y would also correspond to the number of rows in a matrix-array transducer, if each frame is treated as a row. The number of transducers in the linear array is m_x . To group these, we have $M = m_x \times m_y$. In future work [40], we describe the case where multiple frames and multiple optical wavelengths are used.

For a non-separable approach, the complexity is $\mathcal{O}(m_x m_y n_x n_y n_z k_a) = \mathcal{O}(MNk_a)$. The parameter k_a is the ratio of spatial samples (voxels) that must be processed per time-domain sample per transducer channel. In other words, each voxel maps onto k_a time-domain samples per channel. Various implementation design decisions effect k_a .

For a separable approach, the computational complexity is around $\mathcal{O}(MN^{\frac{2}{3}}k)$, where k represents an implementation dependent parameter (either k_a , k_b , k_c or k_d , as described below). The complexity is therefore reduced by an order-of-magnitude compared to a non-separable approach. For example, consider a volume of $100 \times 100 \times 100$ voxels. Here, $N = 100^3$ and $N^{\frac{2}{3}} = 100^2$. This

Table 3.1: Computation time (milliseconds) for simulating 3D volumes based on Propositions 3.1, 3.2 and 3.4. The grid size (number of voxels) was varied. All cases used 256 transducer channels with 1024 output samples per channel. The total execution time includes run-times for the GPU implementations of $\mathcal{G}$ and $\tilde{\mathcal{G}}$, plus computational overhead for memory transfers and CPU processing.

Grid Size	Method	$\mathcal{G}$	$\tilde{\mathcal{G}}$	Overhead	Total
$128 \times 128 \times 128$	Prop. 3.1	4	14	13	31
$256 \times 256 \times 256$	Prop. 3.1	10	14	18	42
$512 \times 512 \times 512$	Prop. 3.1	39	16	102	157
$768 \times 768 \times 768$	Prop. 3.1	48	15	336	399
$128 \times 128 \times 128$	Prop. 3.2	7	24	12	43
$256 \times 256 \times 256$	Prop. 3.2	18	24	45	86
$512 \times 512 \times 512$	Prop. 3.2	30	22	305	357
$768 \times 768 \times 768$	Prop. 3.2	92	19	1001	1112
$128 \times 128 \times 128$	Prop. 3.4	12	99	11	122
$256 \times 256 \times 256$	Prop. 3.4	25	96	20	141
$512 \times 512 \times 512$	Prop. 3.4	91	93	55	239
$768 \times 768 \times 768$	Prop. 3.4	208	92	365	665

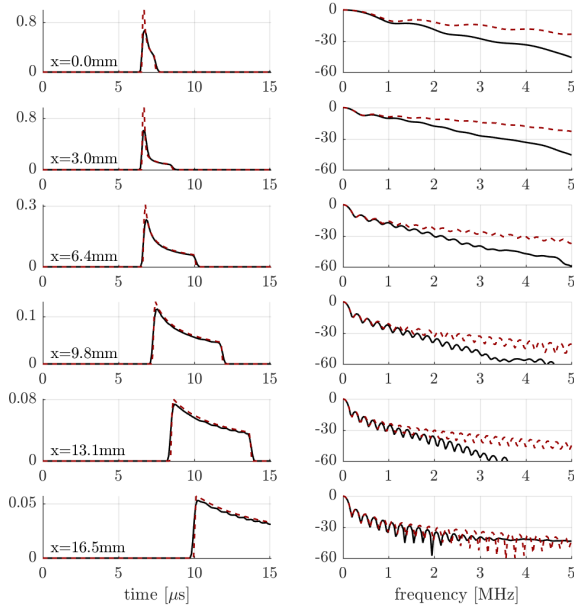


Figure 3.7: Signals from point source at $(x,y,z)=(0,0,10)\text{mm}$, detected by transducer of width $6\text{mm} \times 6\text{mm}$. (solid line) computed using separable approach of Proposition 3.2. (dotted line) computed using Field II. (left) time-domain. (right) frequency domain. Due to the finite grid spacing of 3D voxels in the opto-acoustic source distribution, this results in a low-pass filtering effect of the simulated signals, which accounts for the differences seen here.

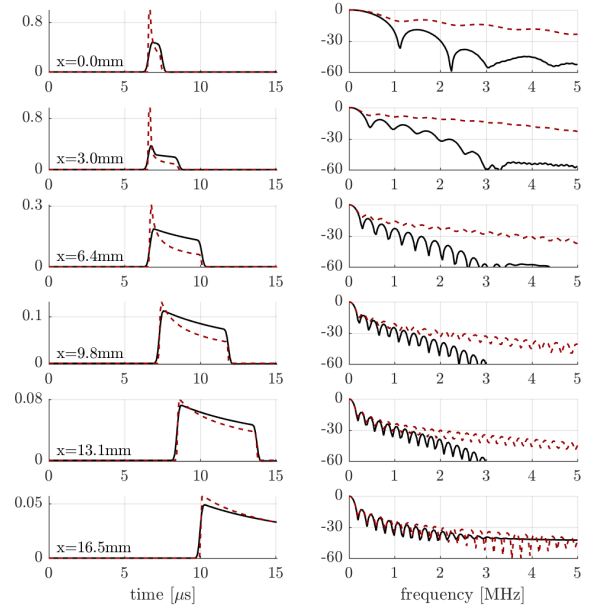


Figure 3.8: Signals from point source at $(x,y,z)=(0,0,10)\text{mm}$, detected by transducer of width $6\text{mm} \times 6\text{mm}$. (solid line) computed using separable far-field approximation of Proposition 3.4. (dotted line) computed using Field II. (left) time-domain. (right) frequency domain. The far-field approximation of Proposition 3.4 results in increased computational performance compared to Proposition 3.2, however the accuracy is reduced.

means that for the separable case there are 100 times fewer operations than with a non-separable approach. In this case, a 100 times speed-up would easily be achievable in practice, and the speed-up would be higher for larger volumes.

The parameter k_a is proportionate to the number of samples required to model the transducer aperture geometry. It is also proportionate to the ratio $\frac{f_s}{f_c}$, where $f_c = \frac{c_0}{\Delta x}$ is the critical sampling rate (described above), $f_s = \frac{n_s}{t_{\max}}$ is the sampling rate used in simulation, n_s is number of time-domain samples, and $t_{\max}$ is the sampling duration. It is assumed that sampling occurs at the critical rate $f_s = f_c$. For a point aperture, k_a is assumed to equal 1.

For the separable approach, during the first application of the operator $\mathcal{G}$, which is an intermediate step, the number of output channels is not the number of transducers m_x (this matches after the second application of $\mathcal{G}$). The number of output positions for the intermediate step is called $m_{x'}$. It is recommended that $m_{x'}$ should be sufficiently greater than m_x to avoid boundary problems, so that the first and final transducers have enough adjacent data for accurate simulation. Using $m_{x'} = 3m_x$ will supply additional padding equal to the length of the array. For Propositions 3.1 or 3.2, the complexity is $\mathcal{O}(m_y(m_{x'}n_xn_z + m_xn_y n_z)k_b)$. Generally, m_x can be assumed to be a constant multiple of $m_{x'}$, so they are the same for complexity purposes. The parameter k_b is

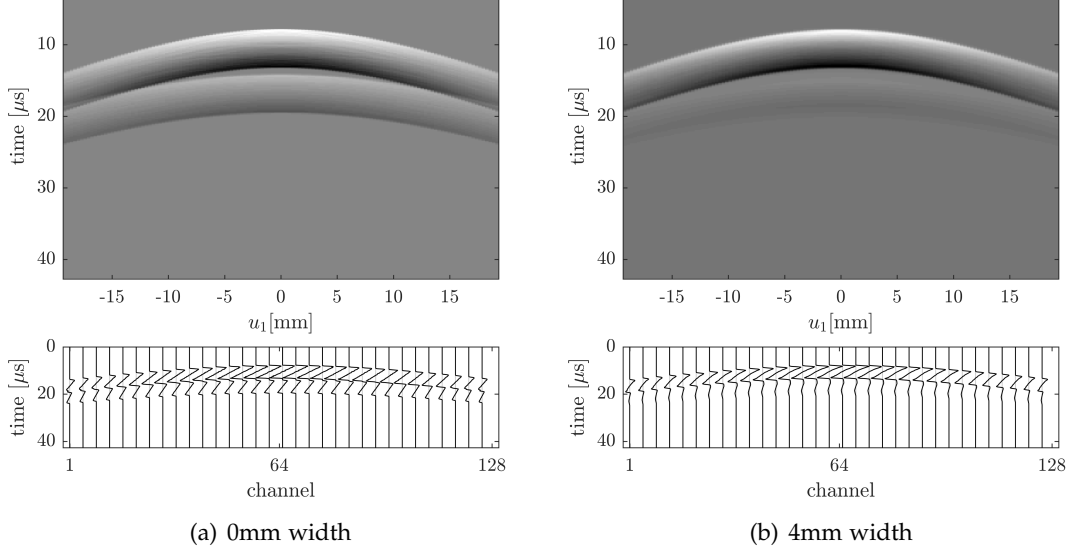


Figure 3.9: Simulated data for linear array. Time domain data is shown graphically (top) and plotted (bottom). The array is positioned as shown in Figure 3.10. The transducer elements are modeled using (a) an ideal point detector and (b) a 4mm wide line aperture. The time-domain plots (bottom) illustrate that each spherical absorber generates an N-shaped waveform, which arrives earlier for the in-plane absorber than the out-of-plane absorber. The out-of-plane waveform is weaker in (b) compared to (a) because the transducer aperture acts as a spatially-dependent filter.

similar to k_a although its implementation may be different. For a point aperture, Proposition 3.2 reduces to Proposition 3.1 and $k_b = 1$. In our implementation of Proposition 3.2, the convolution $\mathcal{G} \circledast f$ is implemented separate from the GPU computation of $\mathcal{G}$, which adds computational overhead with complexity $\mathcal{O}(n_x n_y n_z k_b m_y)$ that becomes dominant in large grid sizes. This is one reason why Proposition 3.4 performs better in Table 3.1 for large grid sizes.

When the far-field approximation of Proposition 3.4 is used, spatial-domain filtering operations are moved to time-domain operations. In this case, k_b would have a constant value of 2, and a new parameter k_c is introduced corresponding to additional time-domain sampling operations. Thus, if k_c is only proportional to the number of output channels, the complexity is changed from $\mathcal{O}(m_y m_x (n_x n_z + n_y n_z) k_b)$ to $\mathcal{O}(m_y m_x (n_x n_z + n_y n_z + k_c))$. This is another reason why Proposition 3.4 can be made faster than Proposition 3.2. Both reduce to approximately the same complexity for Proposition 3.1, where $k_b = k_c = 1$. If it is desired to include the obliquity factor according to Proposition 3.3, since this consists of time-domain operations, it corresponds to a mixture of the k_b and k_c parameters, depending on implementation, and the complexity analysis is similar.

Table 3.1 illustrates run-times measured using our implementation. In Table 3.1, the run-time for $\mathcal{G}$ varies in proportion to grid size because the intermediate data is critically sampled relative to the 3D volume. However, in Table 3.1, the run-time of $\tilde{\mathcal{G}}$ does not change significantly (within each method) with grid size because all tests used a constant $n_s = 1024$. If n_s is increased with grid size, the run-time for $\tilde{\mathcal{G}}$ scales in a similar manner to $\mathcal{G}$. For large grid sizes, the run-times for

Table 3.2: Computational complexity of simulation models.

Method	Computational Complexity
Non-separable	$\mathcal{O}(m_x m_y n_x n_y n_z k_a)$
Sep. Exact (Prop. 3.1 & 3.2)	$\mathcal{O}(m_y m_x (n_y n_z + n_x n_z) k_b)$
Sep. Approx. (Prop. 3.4)	$\mathcal{O}(m_y m_x (n_y n_z + n_x n_z + k_c))$
Mixed-domain	$\mathcal{O}(m_y n_z (m_x n_y k_d + n_x \log(n_x n_z)))$

Table 3.3: Symbol names for complexity analysis

Symbol	Description
n_x, n_y, n_z	number of voxels in x -, y - and z -axis
m_x	number of transducers in linear-array
$m_{x'}$	number of intermediate positions
m_y	number of frames (or transducer rows)
k_a, k_b, k_d	spatial samples per output sample
k_c	temporal samples per output sample

$\tilde{\mathcal{G}}$ and $\mathcal{G}$ are significantly faster compared to the computational overhead. In applications such as image reconstruction, where $\tilde{\mathcal{G}}$ and $\mathcal{G}$ (and their adjoints) must be repeated multiple times, the computational overhead becomes less significant because portions of it are performed only once.

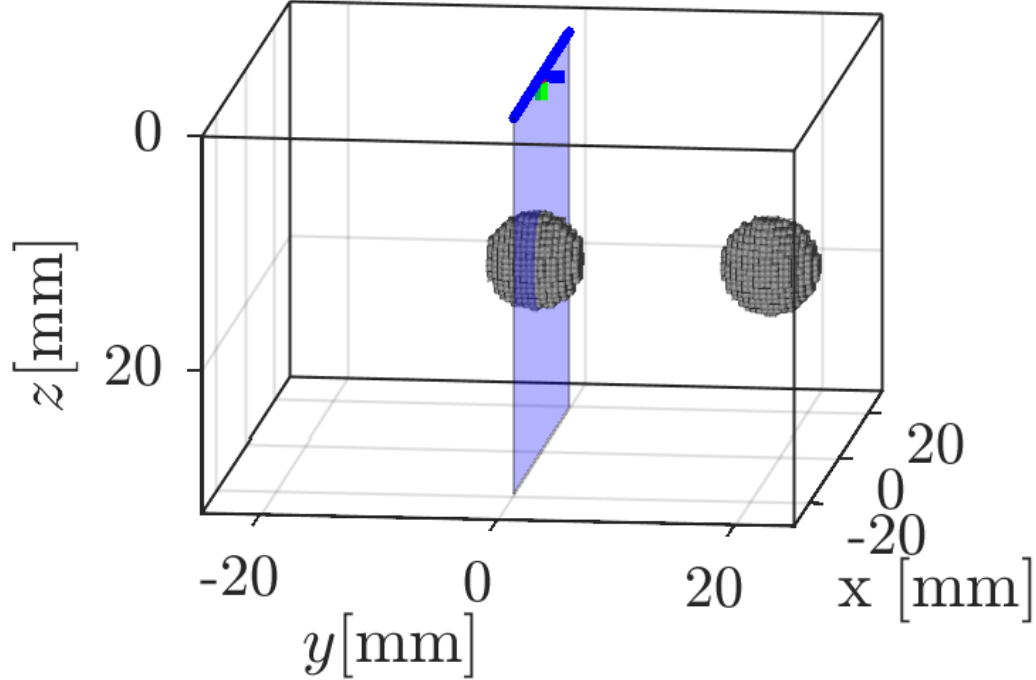


Figure 3.10: 3D volume with spherical absorbers. A linear array (blue line) and the imaging plane (light blue) are shown.

Separable computation can also be performed by separable frequency-domain approaches [17]. In the frequency-domain, this is computationally efficient when transducers are aligned on a grid. This is because the Fast Fourier Transform (FFT) uses spatial sampling at regular intervals. The computational complexity of performing a 2D-FFT for an image of size $n_y \times n_z$ is $\mathcal{O}(n_y n_z \log n_y n_z)$. To perform separable simulation in the frequency-domain, this involves using a pair of two-dimensional cascaded operators (analogous to the cascaded time-domain operators). In each cascaded 2D frequency-domain operation, the space of 2D Fourier data is warped using a non-linear transformation. This can be implemented as interpolation and re-sampling operations, so this does not increase computational complexity, aside from determining coordinate indices of a non-linear function. Convolution with an aperture function, can be performed in the frequency-domain using ordinary multiplication. An inverse 2D-FFT applied to the warped data generates the final output for $\mathcal{G}$.

The frequency-domain output corresponds to the same 2D data expected by $\mathcal{G}$ (see Figure 3.3b). Consequently, a separable time-domain factor can be replaced with its frequency-domain equivalent. The advantage to this replacement is that the frequency-domain version is able to compute data for all transducer positions simultaneously, using the $\mathcal{O}(n \log n)$ FFT complexity.

However, when a linear-array undergoes motion along an arbitrary trajectory, the acquisitions (each coinciding with a laser pulse) occur when the probe has non-uniformly spaced position and orientation. This means that using a frequency-domain version of $\mathcal{G}$ loses its efficiency, since the planes in Figure 3.3a would not line up, unless the probe moves uniformly. The lowest computational complexity would arise when a mixed-domain approach is used, where the first application of $\mathcal{G}$ uses the time-domain approach, and the second application of $\mathcal{G}$ uses the frequency-domain. The computational complexity for this is $\mathcal{O}(m_y n_z (m_x n_y k_d + k_e n_x \log(n_x n_z)))$, where k_d and k_e are implementation dependent parameters. Moreover, convolution of the transducer aperture function can be applied efficiently in the frequency domain using multiplication. In this paper, only the mathematical details for time-domain based operators was discussed. Details for comparing the output of time-domain to frequency-domain (and mixed-domain) simulations is the subject of future work.

Additional considerations can permit modeling of an acoustic lens or cylindrical transducers. For example, the contour path illustrated in Figure 3.4 can be modified to include temporal delays that approximate such effects. In this manner, the geometry for a circularly cylindrical transducer can be modeled using separable operators similar to the approach of Proposition 3.2, which is a subject of further study.

3.6 CONCLUSION

A fast approach to simulate opto-acoustic signal generation in a linear array of rectangular transducer elements was described. Volume integration using a Green's function solution of the acoustic wave equation was shown to be separable into a pair of operators that act along perpendicular directions, which permits fast algorithms for computing opto-acoustic response.

The computational complexity for time-domain simulation of a volume with $N = n_x \times n_y \times n_z$ voxels, as recorded by $M = m_x \times m_y$ transducers, is reduced from $\mathcal{O}(MNk^2)$, in the case where a non-separable approach is used, to $\mathcal{O}(m_x m_y k(n_x n_z + n_y n_z)) \approx \mathcal{O}(MN^{\frac{2}{3}}k)$, where k depends on transducer geometry. A custom GPU-based implementation was used to demonstrate this technique.

3.A APPENDIX

3.A.1 Proof of Proposition 3.1

Proof. First, we examine the Green's function from Equation (3.24), which is

$$g(\mathbf{x}, t) = \frac{1}{4\pi \|\mathbf{x}\|} \delta(t - \|\mathbf{x}\|) = \frac{1}{4\pi t} \delta(t - \|\mathbf{x}\|).$$

It contains $\delta(t - \|\mathbf{x}\|)$, which can be factored according to the sifting property of the delta function[§]. Since $\|\mathbf{x}\|^2 = x_1^2 + (x_2^2 + x_3^2)$, it follows that

$$\delta(t - \|\mathbf{x}\|) = \int_{-\infty}^{\infty} \delta(t - r) \delta(\tau - \rho) d\tau, \quad (3.35)$$

where $r = \sqrt{x_1^2 + \tau^2}$ and $\rho = \sqrt{x_2^2 + x_3^2}$. Therefore,

$$\begin{aligned} h(\mathbf{x}, t) &= \frac{\partial}{\partial t} g(\mathbf{x}, t) \\ &= \frac{1}{4\pi} \frac{\partial}{\partial t} \left(\frac{1}{t} \int \delta(t - r) \delta(\tau - \rho) d\tau \right). \end{aligned} \quad (3.36)$$

From Equation (3.27), the pressure $p(\mathbf{x}, t)$ measured from an acoustic source distribution $\psi(\mathbf{x})$ is

$$\begin{aligned} \mathcal{H}\{\psi\}(\mathbf{x}, t) &= h(\mathbf{x}, t) \underset{\mathbf{x}}{\otimes} \psi(\mathbf{x}) \\ &= \int h(\mathbf{x}', t) \psi(\mathbf{x} - \mathbf{x}') d\mathbf{x}'. \end{aligned}$$

By substituting (3.36), this is equal to

$$\frac{1}{4\pi} \frac{\partial}{\partial t} \iint \frac{1}{t} \delta(t - r') \delta(\tau - \rho') \psi(\mathbf{x} - \mathbf{x}') d\tau d\mathbf{x}', \quad (3.37)$$

where $r' = \sqrt{x_1'^2 + \tau^2}$ and $\rho' = \sqrt{x_2'^2 + x_3'^2}$. Since $d\mathbf{x}' = dx_1' dx_2' dx_3'$, by replacing $dx_2' dx_3'$ with $\rho' d\rho' d\theta'$, where $\theta' \in [0, 2\pi]$, the inner integral can be written in polar coordinates. Equation (3.37) becomes

$$\frac{\partial}{\partial t} \iint \frac{\delta(t - r')}{4\pi t} \underbrace{\int_0^{2\pi} \int_0^\infty \delta(\tau - \rho') \psi(\mathbf{x} - \mathbf{x}') \rho' d\rho' d\theta' d\tau dx_1'}_{\sigma(x_1 - x_1', x_2, \tau)}.$$

§ The sifting property is $\int_{-\infty}^{\infty} \delta(x - y) f(x) dx = f(y)$.

Here, the inner integral is grouped as a function that depends on τ , $\mathbf{x}$ and $\mathbf{x}'$. In the inner integral, ρ' can be eliminated (and replaced with τ) by applying the sifting property to $\delta(\tau - \rho')$. Since $x'_2 = \rho' \cos \theta'$ and $x'_3 = \rho' \sin \theta'$, the inner integral becomes

$$\tau \int_0^{2\pi} \psi \left(\mathbf{x} - \begin{bmatrix} 0 \\ \tau \cos \theta' \\ \tau \sin \theta' \end{bmatrix} - \begin{bmatrix} x'_1 \\ 0 \\ 0 \end{bmatrix} \right) d\theta'. \quad (3.38)$$

To reduce the number of variables that this expression depends on, the coordinate x_3 is set to 0, so the transducer is constrained to the x_1x_2 -plane. We define σ as

$$\sigma(x_1, x_2, \tau) = \tau \int_0^{2\pi} \psi \left(\begin{bmatrix} x_1 \\ x_2 \\ 0 \end{bmatrix} - \begin{bmatrix} 0 \\ \tau \cos \theta \\ \tau \sin \theta \end{bmatrix} \right) d\theta. \quad (3.39)$$

The overall expression (with $x_3 = 0$) becomes

$$\frac{1}{4\pi} \frac{\partial}{\partial t} \iint \frac{\delta(t - r')}{t} \sigma(x_1 - x'_1, x_2, \tau) d\tau dx'_1.$$

Since $r' = \sqrt{x_1'^2 + \tau^2}$, this can be written in polar coordinates where $x'_1 = r' \cos \theta$, $\tau = r' \sin \theta$, and $\theta \in [0, 2\pi]$. By replacing $d\tau dx'_1$ with $r' dr' d\theta$, and using the sifting property on $\delta(t - r')$ to eliminate r' , the expression becomes

$$\begin{aligned} & \frac{1}{4\pi} \frac{\partial}{\partial t} \frac{1}{t} \iint \delta(t - r') \sigma(x_1 - r' \cos \theta, x_2, r' \sin \theta) r' dr' d\theta \\ &= \frac{1}{4\pi} \frac{\partial}{\partial t} \frac{1}{t} \underbrace{t \int \sigma(x_1 - t \cos \theta, x_2, t \sin \theta) d\theta}_{\tilde{s}(x_1, x_2, t)} \\ &= \frac{1}{4\pi} \frac{\partial}{\partial t} \frac{\tilde{s}(x_1, x_2, t)}{t}, \end{aligned} \quad (3.40)$$

where

$$\tilde{s}(x_1, x_2, t) = t \int \sigma \left(\begin{bmatrix} x_1 \\ x_2 \\ 0 \end{bmatrix} - \begin{bmatrix} t \cos \theta \\ 0 \\ t \sin \theta \end{bmatrix} \right) d\theta. \quad (3.41)$$

Here, the three arguments applied to σ are arranged as a column vector to highlight the similarity with (3.39).

Let the operator $\mathcal{G}^{A,b}$ be defined as

$$\mathcal{G}^{A,b}\{\psi\}(u_1, u_2, t) = \mathcal{G}\{\mathcal{T}_{A,b}^{-1}\{\psi\}\}(u_1, u_2, t), \quad (3.42)$$

where

$$\mathcal{G}\{\psi\}(u_1, u_2, t) = t \int_0^{2\pi} \psi \left(\begin{bmatrix} u_1 \\ u_2 - t \cos \theta \\ -t \sin \theta \end{bmatrix} \right) d\theta, \quad (3.43)$$

and

$$\mathcal{T}_{A,\mathbf{b}}^{-1}\{\psi\}(\mathbf{u}) = \psi(A\mathbf{u} + \mathbf{b}).$$

Then $\mathcal{G}^{A,\mathbf{b}}\{\psi\}(u_1, u_2, t)$ is equal to

$$t \int_0^{2\pi} \psi \left(A \begin{bmatrix} u_1 \\ u_2 - t \cos \theta \\ -t \sin \theta \end{bmatrix} + \mathbf{b} \right) d\theta. \quad (3.44)$$

Using Equation (3.39), $\sigma(u_1, u_2, \tau)$ can be written as

$$\mathcal{G}^{A,\mathbf{b}}\{\psi\}(u_1, u_2, \tau),$$

when $A = I$ and $\mathbf{b} = (0, 0, 0)$. Also, from (3.41), $\tilde{s}(u_1, u_2, t)$ can be written as

$$\mathcal{G}^{R,0}\{\sigma\}(u_2, -u_1, t),$$

with the order of arguments u_1 and u_2 reversed, and, using (3.8c),

$$R = R_3(90^\circ) = \begin{bmatrix} 0 & -1 & 0 \\ 1 & 0 & 0 \\ 0 & 0 & 1 \end{bmatrix}.$$

In this equation, the rotation matrix $R_3(90^\circ)$ switches the ordering of the first two elements in a vector that is applied to it, with a sign change. In particular,

$$R_3(90^\circ) \begin{bmatrix} u_2 \\ -u_1 - t \cos \theta \\ -t \sin \theta \end{bmatrix} = \begin{bmatrix} u_1 + t \cos \theta \\ u_2 \\ -t \sin \theta \end{bmatrix}.$$

Here, due to symmetry of integration over θ , the sign change has no impact.

Therefore, the operator $\mathcal{H}^{A,\mathbf{b}}\{\psi\}(u_1, u_2, t)$ can be written

$$\frac{1}{4\pi} \frac{\partial}{\partial t} \left(\frac{1}{t} \mathcal{G}^{R,0}\{\mathcal{G}^{A,\mathbf{b}}\{\psi\}\}(u_2, -u_1, t) \right).$$

This can be written more compactly as

$$\mathcal{H}^{A,\mathbf{b}} = \tilde{\mathcal{G}} \circ \mathcal{G}^{A,\mathbf{b}},$$

where

$$\tilde{\mathcal{G}}\{\psi\}(u_1, u_2, t) = \frac{1}{4\pi} \frac{\partial}{\partial t} \left(\frac{1}{t} \mathcal{G}^{R,0}\{\psi\}(u_2, -u_1, t) \right).$$

This completes the proof. □

3.A.2 Proof of Proposition 3.2

Proof. This proof follows from expanding the convolution integral from Proposition 3.1, when multiplicatively separable aperture f is included. We illustrate this with an expanded version of Equation (3.37) when written as a convolution.

First we observe that for an arbitrary aperture function $f(\mathbf{u})$, the operator $\mathcal{H}_f^{A,\mathbf{b}}\{\psi\}(\mathbf{u}, t)$ can be written as a convolution

$$\begin{aligned}\mathcal{H}_f^{A,\mathbf{b}}\{\psi\}(\mathbf{u}) &= f(\mathbf{u}) \underset{\mathbf{u}}{\circledast} \left(\mathcal{H}^{A,\mathbf{b}}\{\psi\}(\mathbf{u}, t) \right) \\ &= \mathcal{H}\{f \circledast \mathcal{T}_{A,\mathbf{b}}^{-1}\{\psi\}\}(\mathbf{u}, t).\end{aligned}$$

This can be seen from Equation (3.11), where by definition

$$\begin{aligned}\mathcal{H}_f\{\psi\}(\mathbf{x}) &= \underbrace{h(\mathbf{x}, t) \underset{\mathbf{x}}{\circledast} f(\mathbf{x})}_{h_f(\mathbf{x}, t)} \underset{\mathbf{x}}{\circledast} \psi(\mathbf{x}) \\ &= h_f(\mathbf{x}, t) \underset{\mathbf{x}}{\circledast} \psi(\mathbf{x}).\end{aligned}$$

In the context of separability, we already know from Proposition 3.1 that the impulse response $\mathcal{H}$ is separable. Therefore, if we define

$$\psi_f^{A,\mathbf{b}}(\mathbf{x}) = \psi^{A,\mathbf{b}}(\mathbf{x}) \underset{\mathbf{x}}{\circledast} f(\mathbf{x}),$$

then $\mathcal{H}\{\psi_f^{A,\mathbf{b}}\}$ can also be computed by separable cascade per Proposition 3.1.

We now need to show that f_1 and f_2 can be paired with each of the cascaded operators. Since $f(\mathbf{u}) = f_1(u_1)f_2(u_2)\delta(u_3)$, it follows that

$$\psi^{A,\mathbf{b}}(\mathbf{u}) \underset{\mathbf{u}}{\circledast} f(\mathbf{u}) = \psi^{A,\mathbf{b}}(\mathbf{u}) \underset{u_1}{\circledast} f_1(u_1) \underset{u_2}{\circledast} f_2(u_2). \quad (3.45)$$

Here, we have used the relationship $f_1(u_1)f_2(u_2) = f_1(u_1)\delta(u_2) \underset{u_1, u_2}{\circledast} f_2(u_2)\delta(u_1)$.

The operator $\mathcal{G}$ can be written as a 2D spatial convolution with a cylindrical kernel (or a 3D spatial convolution with a ring shaped kernel). This can be seen by manipulating equation (3.43), first by integrating with $\delta(t - \rho)$ to add the variable ρ (which had been removed earlier by sifting),

and then substituting $du'_2 du'_3 = \rho d\theta d\rho$. Thus

$$\begin{aligned}
\mathcal{G}\{\psi\}(u_1, u_2, t) &= t \int_0^{2\pi} \psi \left(\begin{bmatrix} u_1 \\ u_2 - t \cos \theta \\ -t \sin \theta \end{bmatrix} \right) d\theta \\
&= \rho \int_0^\infty \int_0^{2\pi} \delta(t - \rho) \psi \left(\begin{bmatrix} u_1 \\ u_2 - \rho \cos \theta \\ -\rho \sin \theta \end{bmatrix} \right) d\theta d\rho \\
&= \iint \delta\left(t - \sqrt{u_2'^2 + u_3'^2}\right) \psi \left(\begin{bmatrix} u_1 \\ u_2 - u'_2 \\ 0 - u'_3 \end{bmatrix} \right) du'_2 du'_3 \\
&= \left[\delta\left(t - \sqrt{u_2^2 + u_3^2}\right) \underset{u_2, u_3}{\circledast} \psi(u_1, u_2, u_3) \right]_{u_3=0} \\
&= \left[(\delta(u_1) \delta(t - \|\mathbf{u}\|)) \underset{\mathbf{u}}{\circledast} \psi(\mathbf{u}) \right]_{u_3=0}.
\end{aligned} \tag{3.46}$$

With similar form to equation (3.37), we can write $\mathcal{G}^{R,0}\{\mathcal{G}\{\psi_f^{A,\mathbf{b}}(\mathbf{u})\}\}(u_1, u_2, t)$ as

$$\left[\delta\left(t - \left\| \begin{bmatrix} u_1 \\ \tau \end{bmatrix} \right\| \right) \underset{u_1, \tau}{\circledast} \delta\left(\tau - \left\| \begin{bmatrix} u_2 \\ u_3 \end{bmatrix} \right\| \right) \underset{u_2, u_3}{\circledast} \psi_f^{A,\mathbf{b}}(\mathbf{u}) \right]_{u_3=0}.$$

Rearranging, and using Equation (3.45), this is equal to

$$\left[\left(f_1(u_1) \underset{u_1}{\circledast} \delta\left(t - \left\| \begin{bmatrix} u_1 \\ \tau \end{bmatrix} \right\| \right) \right) \underset{u_1, \tau}{\circledast} \left(f_2(u_2) \underset{u_2}{\circledast} \delta\left(\tau - \left\| \begin{bmatrix} u_2 \\ u_3 \end{bmatrix} \right\| \right) \underset{u_2, u_3}{\circledast} \psi^{A,\mathbf{b}}(\mathbf{u}) \right) \right]_{u_3=0}.$$

Thus,

$$\mathcal{G}^{R,0}\{\mathcal{G}\{\psi_f^{A,\mathbf{b}}(\mathbf{u})\}\} = \mathcal{G}_{f_1}^{R,0}\{\mathcal{G}_{f_2}\{\psi^{A,\mathbf{b}}(\mathbf{u})\}\}.$$

Since $\tilde{\mathcal{G}} = \frac{1}{4\pi} \frac{\partial}{\partial t} \frac{1}{t} \mathcal{G}^{R,0}$, which can be performed independently from the convolution, this yields $\tilde{\mathcal{H}}_f^{A,\mathbf{b}}$ and the proof is complete. $\square$

3.A.3 Proof of Proposition 3.3

Proof. This proof breaks down into showing the following three cases individually, and their combination yields the full $\mathcal{H}_f^{A,\mathbf{b}}$:

- i.) $\overline{\mathcal{H}}^{A,\mathbf{b}}\{\psi\}(u_1, u_2, t) = [\overline{h}(\mathbf{u}) \underset{\mathbf{u}}{\circledast} \psi(T_{A,\mathbf{b}}(\mathbf{u}))]_{u_3=0}$
- ii.) $\overline{\mathcal{H}}_f\{\psi\}(u_1, u_2, t) = \overline{\mathcal{H}}\{\psi\}(u_1, u_2, t) \underset{u_1, u_2}{\circledast} f(u_1, u_2)$
- iii.) $\overline{\mathcal{H}}\{\psi\}(u_1, u_2, t) = \frac{1}{t} \mathcal{H}\{\tilde{\psi}\}(u_1, u_2, t)$

Case i.) This follows from the proofs of Sections 3.3.1 and 3.3.2, where the reasoning is unchanged by the presence of the obliquity factor. Thus the separable cascade remains unchanged by the presence of rotation and translation.

Case ii.) This follows from the properties of convolution, when the aperture function f is included. Since the aperture is flat, the 3D convolution reduces to a 2D convolution. Since $\overline{\mathcal{H}}_f\{\psi\}(u_1, u_2, t) = \overline{h}_f(\mathbf{u}, t) \underset{\mathbf{u}}{\circledast} \psi(\mathbf{u})$, we only need to confirm that $\overline{h}_f(\mathbf{u}, t)$ remains separable when aperture f is present. Accordingly,

$$\begin{aligned}\overline{h}_f(\mathbf{u}, t) &= \overline{h}(\mathbf{u}, t) \underset{\mathbf{u}}{\circledast} f(\mathbf{u}) \\ &= \overline{h}(\mathbf{u}, t) \underset{\mathbf{u}}{\circledast} f(u_1, u_2) \delta(u_3) \\ &= \overline{h}(\mathbf{u}, t) \underset{u_1, u_2}{\circledast} f(u_1, u_2).\end{aligned}$$

This implies that when the obliquity factor is included, proper convolution with the aperture function is preserved.

Case iii.) In this case, the simplification also arises because the transducer is flat. For a general rotated frame, $\hat{\mathbf{n}}$ can be any unit vector. The operator $\overline{\mathcal{H}}$, as defined in Equation (3.17), can be written of a sum of three components, resulting from the dot product in $\mathbf{x} \cdot \hat{\mathbf{n}}$. Thus,

$$\begin{aligned}\overline{\mathcal{H}}\{\psi\}(\mathbf{x}, t) &= [h(\mathbf{x}, t) \alpha(\mathbf{x})] \underset{\mathbf{x}}{\circledast} \psi(\mathbf{x}) \\ &= \left[h(\mathbf{x}, t) \frac{\mathbf{x} \cdot \hat{\mathbf{n}}}{\|\mathbf{x}\|} \right] \underset{\mathbf{x}}{\circledast} \psi(\mathbf{x}) \\ &= \sum_i \left([h(\mathbf{x}, t) \alpha_i(\mathbf{x})] \underset{\mathbf{x}}{\circledast} \psi(\mathbf{x}) \right),\end{aligned}$$

where $\alpha_i(\mathbf{x}) = \frac{x_i n_i}{\|\mathbf{x}\|}$. When $\hat{\mathbf{n}} = (0, 0, 1)$, which is the case when signals are measured in the local frame F_P , then the summation reduces to a single term, and $\alpha(\mathbf{x}) = \frac{x_3}{\|\mathbf{x}\|}$.

This is always the case for the local coordinate system $\mathbf{u}$, where the transducer is in the plane $u_3 = 0$. The aperture function is $f(\mathbf{u}) = f(u_1, u_2) \delta(u_3)$. When $f(\mathbf{u})$ is convolved with $\overline{h}(\mathbf{u})$, the component $\hat{\mathbf{e}}_3 \cdot (\mathbf{u} - \mathbf{u}')$ will always be equal to u_3 due to the factor $\delta(u_3)$.

From the convolution, we have

$$\begin{aligned}\overline{\mathcal{H}}\{\psi\}(u_1, u_2, t) &= \left[\overline{h}(\mathbf{u}, t) \underset{\mathbf{u}}{\circledast} \psi(\mathbf{u}) \right]_{u_3=0} \\ &= \left[\left(h(\mathbf{u}, t) \frac{u_3}{\|\mathbf{u}\|} \right) \underset{\mathbf{u}}{\circledast} \psi(\mathbf{u}) \right]_{u_3=0} \\ &= \left[\int h(\mathbf{u}', t) \frac{u_3'}{\|\mathbf{u}'\|} \psi(\mathbf{u} - \mathbf{u}') d\mathbf{u} \right]_{u_3=0}\end{aligned}$$

which (because $u_3 = 0$) is equal to

$$\int \frac{h(\mathbf{u}', t)}{\|\mathbf{u}'\|} u'_3 \underbrace{\psi \left(\begin{bmatrix} u_1 - u'_1 \\ u_2 - u'_2 \\ -u'_3 \end{bmatrix} \right)}_{\tilde{\psi}(u_1 - u'_1, u_2 - u'_2, -u'_3)} d\mathbf{u}',$$

where $\tilde{\psi}(\mathbf{u}) = u_3 \psi(\mathbf{u})$. When grouped this way, it shows that the expression is a convolution applied to $\tilde{\psi}$, evaluated at $(u_1, u_2, 0)$. Since the impulse in $h(\mathbf{u}', t)$ from (3.13) occurs at $t = \|\mathbf{u}'\|$, the factor t can be pulled out as a constant. The expression becomes

$$\frac{1}{t} \left[h(\mathbf{u}, t) \underset{\mathbf{u}}{\otimes} \tilde{\psi}(\mathbf{u}) \right]_{u_3=0}.$$

This implies

$$\overline{\mathcal{H}}\{\psi\}(u_1, u_2, t) = \frac{1}{t} \mathcal{H}\{\tilde{\psi}\}(u_1, u_2, t). \quad (3.47)$$

This completes the proof. $\square$

3.A.4 Proof of Proposition 3.4

Proof. For convenience, in this proof we use xyz -coordinates with $z = u_1$, $x = u_2$, $y = u_3$. This avoids some confusion with the u_1 , u_2 and t variables, which would otherwise switch with the first and second application of $\mathcal{G}$. Since we are only concerned with applying the impulse response on a 2D slice, convolution is limited to x and y variables.

The relationship between (u_1, u_2, t) and (x, y, z) is somewhat nuanced, as indicated by the following substitutions. From Equation (3.46), we can write

$$\begin{aligned} \mathcal{G}_f\{\psi\}(u_1, u_2, t) \\ = \left[g_a(x, y, t) \underset{x, y}{\otimes} \psi(z, x, y) \right]_{x=u_2, y=0, z=u_1}, \end{aligned} \quad (3.48)$$

where

$$g_a(x, y, t) = f_a(x, y) \underset{x, y}{\otimes} \tilde{g}(x, y, t), \quad (3.49)$$

and

$$\tilde{g}(x, y, t) = \delta(t - \sqrt{x^2 + y^2}). \quad (3.50)$$

In order to model a rectangular transducer aperture, we are concerned with a separable cross section of it which is a line segment. Let f_a be an aperture function of width a , corresponding to a line segment located at $y = 0$ in the 2D xy -plane, defined by

$$\begin{aligned} f_a(x, y) &= \text{rect}\left(\frac{x}{a}\right) \delta(y) \\ &= \left(u\left(x + \frac{a}{2}\right) - u\left(x - \frac{a}{2}\right) \right) \delta(y), \end{aligned}$$

where $u(x)$ is the unit step function.

To simplify the mathematics, first we consider geometry for a semi-infinite ray defined by

$$f(x, y) = u(x)\delta(y).$$

This way, we will be able to form a line segment when needed, by adding and subtracting two rays shifted by the aperture width a per

$$\begin{aligned} f_a(x, y) &= f(x + a/2, y) - f(x - a/2, y) \\ &= (u(x + a/2) - u(x - a/2))\delta(y). \end{aligned}$$

Therefore, the convolution that we are now interested in, which is the ray aperture based version of Equation (3.49), is

$$\begin{aligned} f(x, y) \otimes_{x, y} \tilde{g}(x, y, t) &= \int_{\mathbb{R}^2} f(x - x', y - y') \tilde{g}(x', y', t) \, dx' \, dy' \\ &= \int_{\mathbb{R}^2} u(x - x') \delta(y - y') \tilde{g}(x', y', t) \, dx' \, dy'. \end{aligned}$$

The interpretation is that we have to convolve a ray with $\tilde{g}(x, y, t)$, which is a circularly symmetric object. To do this, we will perform the integration for the convolution in polar coordinates.

In polar coordinates, using $x' = r \cos \theta$ and $y' = r \sin \theta$, this becomes

$$\int_0^{2\pi} \int_0^\infty u(x - r \cos \theta) \delta(y - r \sin \theta) \delta(r - t) r \, dr \, d\theta,$$

By using the sifting property[¶] in the variable r , the inner integral disappears, and the expression becomes

$$t \int_0^{2\pi} u(x - t \cos \theta) \delta(y - t \sin \theta) \, d\theta.$$

Since θ is not an isolated variable, the function $\delta(y - t \sin \theta)$ must be transformed before sifting in the variable θ can be applied to this integral^{||}. To isolate θ , we use the change of variables property [48] of the delta function with $\theta = \arcsin(\frac{y}{t})$. This transforms the delta function according to

$$\delta(y - t \sin \theta) \equiv \frac{1}{\sqrt{t^2 - y^2}} \delta\left(\theta - \arcsin\left(\frac{y}{t}\right)\right).$$

[¶] The sifting property is $\int_{-\infty}^\infty \delta(x - y) f(x) \, dx = f(y)$.

^{||} To use the sifting property of the delta function, the coefficient on the variable that is being sifted must be equal to 1 (otherwise using the scaling property of the delta function is necessary). This also applies in more general cases of the form $\delta(\mathbf{g}(\mathbf{x}) - \mathbf{y})$, where the sifting variable $\mathbf{x}$ is found within a function $\mathbf{g}(\mathbf{x})$. Before sifting can properly be applied, the inverse $\mathbf{g}^{-1}$ must be used to isolate $\mathbf{x}$, and the delta function must be scaled. When $\mathbf{g}$ is a one-to-one invertible function, this leads to the scaling relationship of the delta function

$$\delta(\mathbf{g}(\mathbf{x}) - \mathbf{y}) \equiv \frac{1}{|\det \mathbf{g}'(\mathbf{g}^{-1}(\mathbf{y}))|} \delta(\mathbf{x} - \mathbf{g}^{-1}(\mathbf{y})),$$

where $\mathbf{g}'$ is a Jacobian derivative (see Equation 2.99 and Section 2.9 of Faris et al. [48] for a rigorous discussion.)

Now, sifting in the variable θ can be applied. For a given value of t , the term $\delta(\theta - \arcsin(\frac{y}{t}))$ is non-zero at two values of θ on the interval $[0, 2\pi]$. This occurs when $\theta = \arcsin(y/t)$, and is valid when $|y| < t$. By trigonometric identity, this means $t \cos \theta = \pm \sqrt{t^2 - y^2}$. This dual-value causes integration to split into two semi-circular pieces. The integral reduces to

$$\begin{aligned} & \frac{t}{\sqrt{t^2 - y^2}} \left(u\left(x + \sqrt{t^2 - y^2}\right) + u\left(x - \sqrt{t^2 - y^2}\right) \right) \\ & \times \left(u(y + t) - u(y - t) \right). \end{aligned} \quad (3.51)$$

Here, the expression $u(x + \sqrt{t^2 - y^2})$ is a step function that is shifted by an amount equal to the left half of a circle of radius t . The expression $u(x - \sqrt{t^2 - y^2})$ is a step function shifted for the right half of the circle. Since complex values are not allowed, then $|y|$ must be less than or equal to t . This is accomplished by including a factor of $(u(y + t) - u(y - t))$.

Recall that equation (3.51) was developed using the ray aperture $f(x, y)$ to simplify the mathematics. Now, we can consider the line segment aperture $f_a(x, y)$. This means adding and subtracting equation (3.51) when it is shifted by $-\frac{a}{2}$ and $\frac{a}{2}$. The resulting form of Equation (3.49) is written

$$\begin{aligned} g_a(x, y, t) = & \\ & \frac{t}{\sqrt{t^2 - y^2}} \left(u(y + t) - u(y - t) \right) \left[\text{rect}\left(\frac{x + \sqrt{t^2 - y^2}}{a}\right) + \text{rect}\left(\frac{x - \sqrt{t^2 - y^2}}{a}\right) \right]. \end{aligned}$$

Equation (3.52a) corresponds to a solid object (not an outlined object). This can be seen because the rect function has a width equal to a . Therefore, due to the width of the transducer, the 2D spatial convolution $g_a(x, y, t) \underset{x, y}{\circledast} \psi(x, y)$ is not sparse, which leads to some inefficiency.

Convolution with an object that is sparse has only a few non-zero points that must be sampled and multiplied. The dense spatial convolutions can be avoided if there is a time-domain filtering operation that “fills in” points that have been spatially sampled sparsely. As it turns out, the time derivative of an approximation of equation (3.52a) is sparse spatially, and integration in the time-domain can be used to compute the convolution efficiently.

A far-field approximation can simplify equation (3.52a) by assuming small transducer aperture width a relative to working distances. To arrive at this approximation, equation (3.52a) is written in expanded form as

$$\begin{aligned} & t \int_{x'=-\infty}^{\infty} \int_{y'=-t}^t \frac{\psi(x - x', y - y')}{\sqrt{t^2 - y'^2}} \\ & \times \left[\int_{-\frac{a}{2}}^{\frac{a}{2}} \delta\left(x' - x'' + \sqrt{t^2 - y'^2}\right) dx'' \right. \\ & \left. + \int_{-\frac{a}{2}}^{\frac{a}{2}} \delta\left(x' - x'' - \sqrt{t^2 - y'^2}\right) dx'' \right] dx' dy'. \end{aligned}$$

By examining the inner integrals above, over the region of integration $|x''| \ll \frac{a}{2}$. From the delta functions, the condition for non-zero that must be met is $(x' - x'') \pm \sqrt{t^2 - y'^2} = 0$. Also, if it is assumed that $|x''| < a \ll |x'|$ (i.e. if x'' is small), then we can use the approximation $x' - x'' \approx x'$. This implies that we can also use the approximation $\sqrt{t^2 - y'^2} \approx |x'|$ for the term in the denominator, when x' is not too small (i.e. if $x' \geq a$). Otherwise (if $x' \leq a$), since the integration with x'' is performed over the interval $[-\frac{a}{2}, \frac{a}{2}]$, which has a width of a , then the denominator can be replaced with a . In either case, the denominator no longer has the dependence on t or y' , which leads to simplification in the next step.

Therefore, an approximation for g_a is

$$g_a(x, y, t) \approx \frac{t}{\gamma(x)} \text{rect}\left(\frac{y}{2t}\right) \text{rect}\left(\frac{x \pm \sqrt{t^2 - y^2}}{a}\right), \quad (3.52a)$$

where

$$\gamma(x) = \begin{cases} |x| & \text{if } |x| \geq a, \\ a & \text{otherwise.} \end{cases} \quad (3.52b)$$

When used in spatial convolution, the factor t remains constant, and it can be factored out and processed independently from the spatial convolution. To compute g_a , a step of integration and differentiation, which cancel each other out, can be placed between multiplication and division by t . This yields the identity

$$g_a(x, y, t) = t \int_0^t \frac{\partial}{\partial t} \left(\frac{1}{t} g_a(x, y, t) \right) dt. \quad (3.53)$$

Now we return to considering a ray aperture rather than a line segment. For a ray aperture, (i.e., by applying the approximation to Equation (3.51)), the approximation is

$$\frac{t}{\gamma(x)} \left(u\left(x + \sqrt{t^2 - y^2}\right) + u\left(x - \sqrt{t^2 - y^2}\right) \right) \left(u(y + t) - u(y - t) \right).$$

Observe that here the factor $\frac{1}{\gamma(x)}$ does not depend on t . We divide (3.54) by t , compute its time-derivative, and label the result as $\zeta(x, y, t)$. This is a sparse object, shown in Figure 3.4a, which is equal to

$$\begin{aligned} \zeta(x, y, t) = & \frac{t}{\sqrt{t^2 - y^2}} \left(\delta\left(x + \sqrt{t^2 - y^2}\right) - \delta\left(x - \sqrt{t^2 - y^2}\right) \right) \\ & \times \frac{1}{\gamma(x)} \left(u(y + t) - u(y - t) \right) \\ & + \frac{1}{\gamma(x)} \left(\delta(y - t) + \delta(y + t) \right) u(x). \end{aligned} \quad (3.54)$$

For the line segment aperture, this can be used to compute $\frac{\partial}{\partial t} \left(\frac{1}{t} \mathcal{G}_a \right)$ from $\varsigma(x, y, t)$ as

$$\begin{aligned} \frac{\partial}{\partial t} \left(\frac{1}{t} \mathcal{G}_a \{ \psi \} (u_1, u_2, t) \right) \\ = \left[h_a(x, y, t) \underset{x, y}{\circledast} \psi(u_1, x, y) \right]_{x=u_2, y=0} \end{aligned}$$

where

$$h_a(x, y, t) = \varsigma \left(x + \frac{a}{2}, y, t \right) - \varsigma \left(x - \frac{a}{2}, y, t \right).$$

Writing out the convolution integral, it becomes

$$\int_{\mathbb{R}^2} h_a(x', y', t) \psi(u_1, u_2 - x', 0 - y') dx' dy'.$$

This is integrated over $dx' dy'$. However, h_a consists of 6 contours: two positive circular arcs, two negative circular arcs, and two lines. The circular arcs are of the form

$$\frac{1}{\gamma(x \pm a)} \frac{t}{\sqrt{t^2 - y^2}} \delta \left(x \pm a \pm \sqrt{t^2 - y^2} \right) u(x \pm a).$$

This can be integrated in polar coordinates after a change of coordinates. Thus

$$\begin{aligned} \int_{\mathbb{R}^2} \frac{t}{\sqrt{t^2 - y'^2}} \delta \left(x' - \sqrt{t^2 - y'^2} \right) u(x') \frac{1}{\gamma(x')} \psi(u_1, u_2 - a - x', -y') dx' dy' \\ = \int_0^\infty \int_k^{\pi+k} \delta(t - r) \frac{\psi(u_1, u_2 - a - \cos \theta, \sin \theta)}{\tilde{\gamma}(r, \theta)} r dr d\theta \\ = \int_k^{\pi+k} \frac{\psi(u_1, u_2 - a - \cos \theta, \sin \theta)}{\tilde{\gamma}(t, \theta)} d\theta. \end{aligned}$$

In this equation, we use $\tilde{\gamma}(t, \theta) = \gamma(|t \cos \theta|)$. In this manner, the four arcs of $\frac{\partial}{\partial t} \frac{1}{t} \mathcal{G}_a$ can be computed as listed in Proposition 3.4. Similarly the two lines can also be computed in this manner. This completes the proof. $\square$

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ABSTRACT

Opto-acoustic imaging systems detect acoustic waves produced by optical absorption to visualize molecular contrast in biological tissue. This permits non-invasive vascular assessment of benign and malignant tumors. In this article, we describe a framework to iteratively determine the motion of an opto-acoustic probe during a minimization-based image reconstruction process. The probe emits light and uses an ultrasonic transducer array to acquire data for cross-sectional slices of tissue. To improve visibility, our technique uses multiple 2D slices to perform 3D volumetric reconstruction. Our model includes wavelength-specific optical absorption, position-dependent illumination and a realistic transducer element geometry. We investigate this technique using simulated, experimentally collected, and clinically acquired data. By performing 3D image reconstruction on a digital phantom, we demonstrate estimation of elevational probe motion without external sensors. We compare images of a benign lesion from a clinical breast imaging study and observe significant artifact reduction and contrast-to-background ratio improvement using our technique. The approach has potential to improve opto-acoustic image visibility for assessment of breast cancer or other diseases.

LIST OF SYMBOLS

Table 4.1: List of symbols

Symbol	Description
$\mathbf{y}_j \in \mathbb{R}^{n_m}$	measured data for j -th frame $\mathbf{y} = \text{vec}([\mathbf{y}_1, \mathbf{y}_2, \dots, \mathbf{y}_{n_f}])$
$\mathbf{x}_i \in \mathbb{R}^{n_v}$	volume fraction abundance of i -th chromophore $X = [\mathbf{x}_1, \mathbf{x}_2, \dots, \mathbf{x}_{n_\mu}] \in \mathbb{R}^{n_v \times n_\mu}$ $\mathbf{x} = \text{vec}(X) \in \mathbb{R}^{(n_v n_\mu)}$
$H \in \mathbb{R}^{(n_m n_f) \times (n_v n_\mu)}$	overall system matrix $H = \begin{bmatrix} H_1 \\ \vdots \\ H_{n_f} \end{bmatrix}$
$H_j \in \mathbb{R}^{(n_m) \times (n_v n_\mu)}$	system matrix for j -th frame $H_j = H_0 \Phi_{\lambda_j} T_{\mathbf{p}_j} M_{\lambda_j}$
$H_0 \in \mathbb{R}^{n_m \times n_v}$	acoustic response matrix $H_0 = F_0 G_0$
$M_{\lambda_j} \in \mathbb{R}^{(n_v) \times (n_v n_\mu)}$	absorption matrix for wavelength λ_j $M_{\lambda_j} = \mathbf{m}_{\lambda_j} \otimes I_{n_v}$
$\Phi_{\lambda_j} \in \mathbb{R}^{n_v \times n_v}$	optical illumination matrix for wavelength λ_j $\Phi_{\lambda_j} = \text{diag}(\boldsymbol{\varphi}_{\lambda_j})$
$T_{\mathbf{p}_j} \in \mathbb{R}^{n_v \times n_v}$	transformation matrix for configuration $\mathbf{p}_j$
$\mathbf{p}_j \in \mathbb{R}^{n_p}$	configuration parameters for j -th frame $\mathbf{p} = \text{vec}([\mathbf{p}_1, \mathbf{p}_2, \dots, \mathbf{p}_{n_f}])$
$\Delta \mathbf{p}_j \in \mathbb{R}^{n_p}$	change in configuration for j -th frame $\Delta \mathbf{p} = \text{vec}([\Delta \mathbf{p}_1, \Delta \mathbf{p}_2, \dots, \Delta \mathbf{p}_{n_f}])$
$J_{\mathbf{p}_j} \in \mathbb{R}^{n_m \times n_p}$	Jacobian matrix for configuration $\mathbf{p}_j$
$A_j \in \mathbb{R}^{3 \times 3}$	rotation matrix for j -th frame
$\mathbf{b}_j \in \mathbb{R}^3$	translation vector for j -th frame
$\boldsymbol{\theta}_j \in \mathbb{R}^3$	Euler angles for j -th frame (roll, pitch, yaw) $\mathbf{p}_j = \text{vec}([\mathbf{b}_j, \boldsymbol{\theta}_j])$
$\boldsymbol{\theta}: \mathbb{R}^{n_v \times n_\mu} \rightarrow \mathbb{R}$	regularization function
$F_0 \in \mathbb{R}^{n_m \times n_{m'}}$	separable factor for in-plane slice
$G_0 \in \mathbb{R}^{n_{m'} \times n_v}$	separable factor for perpendicular slices
$\psi(\lambda, \mathbf{r})$	initial excess acoustic pressure
$\eta(\lambda, \mathbf{r})$	opto-acoustic conversion efficiency

continued ...

...continued

Symbol	Description
$\varphi(\lambda, \mathbf{r})$	radiant fluence
$\mu_a(\lambda, \mathbf{r})$	tissue optical absorption coefficient
$m_i(\lambda)$	optical absorption coefficient of chromophore i
$\chi_i(\mathbf{r})$	volume fraction abundance of chromophore i
$\gamma(\mathbf{r})$	Grüneisen parameter
$y(\lambda, \mathbf{r}, t)$	opto-acoustic signal amplitude
$h(\mathbf{r}, t)$	statio-temporal impulse response
$g'(\mathbf{r}, t)$	ideal impulse response
$f_a(\mathbf{r})$	transducer aperture function
$\alpha(\mathbf{r})$	obliquity factor
$\beta(t)$	electro-mechanical impulse response
$\delta(t)$	Dirac delta function
c_0	speed of sound
t	elapsed time
$\mathbf{r} \in \mathbb{R}^3$	spatial position
λ	optical wavelength
λ_j	index for optical wavelength of j -th frame
$\mathbf{m}_{\lambda_j} \in \mathbb{R}^{n_\mu}$	optical absorption vector at wavelength λ_j
$y_j(\mathbf{r}_l, t)$	time-domain signal of transducer l in frame j
$\psi_j(\mathbf{r})$	initial excess pressure of frame j
$\tau_j(\mathbf{r})$	affine transform function for frame j
I_n	identity matrix of size n
$\otimes$	tensor product
$\odot$	Hadamard product (elementwise multiplication)
$n_v = n_x n_y n_z$	number of voxels (total and along xyz axes)
$n_m = n_s n_c$	number of measurements
n_s	number of samples per channel
n_c	number of channels
n_p	number of configuration parameters per frame
n_f	number of frames
n_μ	number of chromophores
n_λ	number of optical wavelengths

4.1 INTRODUCTION

Recent clinical studies have investigated opto-acoustic imaging (OA) for assessment and diagnosis of breast cancer [1]–[11]. OA helps to visualize cancerous lesions, which are metabolically more active, and tend to have higher vascularity, irregular blood vessels, and decreased oxygen saturation compared to benign lesions and healthy tissue [12]–[16]. By using optical absorption to generate acoustic waves, the technology permits imaging of blood vessels and oxygenation levels in tumors located several centimeters beneath the skin, without using harmful ionizing radiation or injected contrast agents [4].

OA reconstruction involves generating images to visualize the molecular composition of tissue. To achieve this, acoustic transducer measurements are digitally processed to localize acoustic sources based on propagation delays. Using multiple optical wavelengths allows molecular constituents to be determined from their optical absorption spectra. For proper tissue visualization, reconstructed images must have minimal clutter and distortion. Although several analytic inversion formulas exist for OA reconstruction [17]–[21], these generally cause distortion unless a reconstructed region of tissue is fully surrounded by detectors to capture all emitted acoustic waves. Consequently, the effectiveness of analytic reconstruction approaches is limited by tissue surface acquisition because complete acoustic capturing is not possible. To permit more accurate image reconstruction, convex mathematical optimization uses assumptions about spatial smoothness and image sparsity to fit reconstructed images onto measured data [22]–[26]. This can significantly improve contrast and reduce clutter. However, certain types of artifacts remain difficult to suppress, especially in 2D imaging systems.

In 2D imaging, subjects are scanned using a hand-held OA probe that incorporates an ultrasonic linear-array transducer with an integrated light delivery unit [1]–[11]. The light distribution, which depends on the illumination geometry and optical wavelength, cannot easily be confined to a 2D slice of tissue. This results in interfering acoustic waves produced by out-of-plane optical absorbers. Moreover, light intensity attenuates exponentially, which limits optical penetration and decreases image contrast in deep tissue. Obtaining additional surface measurements can potentially improve image contrast, interference suppression, and acoustic source localization. However, with free-hand acquired data, this requires the linear array’s position and orientation to be known and included in the reconstruction model. Consequently, there is a need for approaches that efficiently incorporate a probe’s trajectory into 3D opto-acoustic image reconstruction.

In this article, we propose a method to reduce artifact and reconstruct 3D images, which simultaneously solves motion of an OA probe. This enables volumetric reconstruction from multiple 2D slices, which helps suppress interference and improve contrast in 2D imaging. The approach uses sequential convex optimization, and is based on fitting measured acoustic data onto a model’s predicted response. We propose a novel model where a wavelength-specific light distribution is delivered from the probe’s coordinate frame, and predicted acoustic signals are simulated based on 3D molecular composition of tissue. Fast computation is developed using a

separable acoustic response matrix, described in our earlier work [27], which includes the array's position and orientation. We demonstrate reconstruction of 2D and 3D images with improved image quality compared to a formula-based approach.

To our best knowledge, this is the first work involving OA, where reconstruction and motion tracking are solved simultaneously, using a combined minimization approach. In the literature, numerous OA reconstruction approaches have been studied [17]–[26], including formula-based back-projection [17]–[20] and mathematical optimization [22]–[26]. However, these involve different processing and assumptions compared to our approach. Previous methods have been considered to estimate non-rigid deformation with internal tissue motion using L1 optical flow [28], [29], but this is different from solving probe motion and requires many additional variables. In ultrasound, motion tracking has been well studied [30]–[38], but previous sensor-free approaches involving ultrasonic speckle correlation are not fully applicable to OA. Our approach, which is applicable even in the presence of interference specific to OA, was inspired by combined alignment and reconstruction used in other modalities [39] and image processing [40]–[42].

This article is organized as follows. Section 4.2.1 provides theoretical background for opto-acoustic signal generation. Section 4.2.2 describes image reconstruction based on convex mathematical optimization. In Section 4.3, we develop a system model, which simulates opto-acoustic signals for multiple 2D slices. Using this model, in Section 4.4 we develop an algorithm for 3D image reconstruction and motion tracking. Section 4.5 describes the results and implementation. Additional results are provided as Supplemental Materials. Discussion is provided in Section 4.6. We conclude in Section 4.7. Table 4.1 lists symbols used throughout this work.

4.2 BACKGROUND

4.2.1 Opto-acoustic signals

In opto-acoustic imaging, a probe delivers a rapid pulse of light, at *optical wavelength* λ , to the tissue surface. The *radiant fluence* $\varphi(\lambda, \mathbf{r})$ is the amount of light that reaches position $\mathbf{r}$ within the tissue. When light is absorbed, it is converted to an acoustic source distribution called the *initial excess pressure* $\psi(\lambda, \mathbf{r})$, which subsequently propagates as acoustic waves. This is equal to

$$\psi(\lambda, \mathbf{r}) = \eta(\lambda, \mathbf{r}) \varphi(\lambda, \mathbf{r}), \quad (4.1)$$

where $\eta(\lambda, \mathbf{r})$ is the *opto-acoustic conversion efficiency*, which is given by

$$\eta(\lambda, \mathbf{r}) = \gamma(\mathbf{r}) \mu_a(\lambda, \mathbf{r}). \quad (4.2)$$

Here, $\eta(\lambda, \mathbf{r})$ is the product of the tissue *optical absorption coefficient* $\mu_a(\lambda, \mathbf{r})$, which describes conversion of light to heat; and, the *Grüneisen parameter* $\gamma(\mathbf{r})$, which relates added heat to excess pressure. In tissue, γ typically has a small spatial variation, and is often assumed to be constant. The parameter μ_a depends on the abundance of light-absorbing molecules called *chromophores*, which are spatially distributed based on the tissue composition, and can have widely different

wavelength-specific optical properties from each other. In multi-wavelength imaging, this enables visualization of molecular tissue contrast. The tissue optical absorption μ_a is determined by a weighted linear combination

$$\mu_a(\lambda, \mathbf{r}) = \sum_i m_i(\lambda) \chi_i(\mathbf{r}), \quad (4.3)$$

where $m_i(\lambda)$ is the optical absorption at wavelength λ , for the i -th chromophore, and $\chi_i(\mathbf{r})$ is its *volume fraction abundance*.

In an acoustically homogeneous medium, pressure waves due to $\psi(\mathbf{r}, \lambda)$ propagate radially outward from $\mathbf{r}$ at a constant speed of sound c_0 . The signal measured by an acoustic transducer at position $\mathbf{r}_0$, at time t , is

$$y(\lambda, \mathbf{r}_0, t) = \int_{\mathbb{R}^3} h(\mathbf{r}_0 - \mathbf{r}, t) \psi(\lambda, \mathbf{r}) \, d\mathbf{r}. \quad (4.4)$$

Here, the *spatio-temporal impulse response* for a transducer measurement is

$$h(\mathbf{r}, t) = \int_{-\infty}^{\infty} \int_{\mathbb{R}^3} g'(\tilde{\mathbf{r}}, \tilde{t}) f_a(\mathbf{r} - \tilde{\mathbf{r}}) \alpha(\tilde{\mathbf{r}}) \beta(t - \tilde{t}) \, d\tilde{\mathbf{r}} \, d\tilde{t}, \quad (4.5)$$

where

$$g'(\mathbf{r}, t) = \frac{\partial}{\partial t} \frac{\delta(\|\mathbf{r}\| - c_0 t)}{4\pi t} \quad (4.6)$$

is the *ideal impulse response* for an infinitesimally-sized omni-directional transducer. In this equation, $\delta(t)$ is the Dirac delta function. In (4.5), the *transducer aperture function* $f_a(\mathbf{r})$ models the element geometry. For rectangular elements, this is

$$f_a(\mathbf{r}) = \text{rect}\left(\frac{r_1}{a_1}, \frac{r_2}{a_2}\right) \delta(r_3), \quad (4.7)$$

where a_1 and a_2 represent the element length and width, and the element is oriented normal to the r_3 -axis, with coordinates $\mathbf{r} = (r_1, r_2, r_3)$. The *obliquity factor*

$$\alpha(\mathbf{r}) = \frac{|\mathbf{r} \cdot \hat{\mathbf{n}}|}{\|\mathbf{r}\|} \quad (4.8)$$

models the transducer directionality. Here, $\hat{\mathbf{n}}$ is the outward normal to the transducer at $\mathbf{r}$. For an omni-directional transducer, which does not include directionality, $\alpha(\mathbf{r})$ is set to 1. The *electro-mechanical impulse response* $\beta(t)$ describes the spatially-independent bandwidth of the receiving element and system electronics. To model an ideal wide-band response, where $\beta(t)$ has no contribution, $\beta(t)$ can be set to $\delta(t)$.

4.2.2 Image reconstruction using mathematical optimization

Images of tissue can be reconstructed from acquired sensor measurements using mathematical optimization algorithms [22]–[26], [43]–[55]. This involves finding an unknown $\mathbf{x}$ that minimizes error between a *measured response* $\mathbf{y}$ and a *predicted response* $\tilde{\mathbf{y}} = H\mathbf{x}$. Here, the *system matrix* H

models the responses that are predicted to be measured for any given image $\mathbf{x}$. Representing the response of a linear system by H generally involves converting continuous equations to discretized matrix form. For example, H can implement transducers using equation (4.5) to model an OA system, as detailed in Section 4.3.2 to represent our model.

To solve $\mathbf{x}$, a general approach that covers many applications in image and signal processing [44]–[47], [50]–[52] involves minimizing a convex optimization problem of the form

$$\begin{aligned} & \text{minimize} && \|\mathbf{H}\mathbf{x} - \mathbf{y}\|_2^2 + \vartheta(\mathbf{x}) \\ & \text{subject to} && \mathbf{x} \in \mathcal{C} \end{aligned} \tag{4.9}$$

When an optimization problem is convex, its *global optimal solution* can be found iteratively by computing a converging sequence of solutions. Here, $\|\mathbf{H}\mathbf{x} - \mathbf{y}\|_2^2$ is a *fidelity function* that matches measured data to the model. The *regularization function* $\vartheta(\mathbf{x})$ penalizes unwanted solutions, occurring due to noise amplification, which otherwise might minimize (4.9). Different regularization functions can be used depending on anticipated properties of the reconstructed image. Generally, $\vartheta(\mathbf{x})$ has a corresponding *proximal operator* that can be computed efficiently, as described in Appendix A. For example, in ℓ_1 -minimization, $\vartheta(\mathbf{x})$ promotes sparse solutions, with few non-zero elements, by using an ℓ_1 -norm $\|\cdot\|_1$. The ℓ_1 proximal operator is a simple soft-thresholding function. Our approach uses total-variation (TV) regularization [26], [45], [46], which involves a weighted ℓ_1 -norm to enforce sparseness in the spatial gradient of $\mathbf{x}$, promoting image smoothness. This helps to reduce noise when visualizing tissue. In equation (4.9), the convex set $\mathcal{C}$ represents *constraints*, restricting the allowed values of $\mathbf{x}$. For example, $\mathcal{C} = \{x \mid x \geq 0\}$ will permit only non-negative values in $\mathbf{x}$, which is useful when the unknown variable must be positive.

Equation (4.9) can be solved by several techniques, including the alternating direction method of multipliers (ADMM) [49], [52], and accelerated proximal gradient (APG) [26], [44]–[47], [50]–[52]. Mathematical details of these minimization algorithms, as used in our approach, are provided in Appendix A.

To perform motion tracking, additional variables representing probe position and orientation must be solved. When these are included, the system matrix H becomes non-linear (with respect to these variables), which makes solving equation (4.9) more difficult compared to conventional image reconstruction. In this case, *sequential convex optimization* [39]–[42], [56], [57] can be used, which iteratively computes a sequence of linearized convex subproblems, as described in Section 4.4.3.

4.3 SYSTEM MODEL

4.3.1 Frames collected by linear array

In this work, a system model is developed by extending equation (4.4) to multiple frames. This is applicable in 2D clinical imaging, where a hand-held probe with linear transducer array is manually scanned along the surface of a subject’s tissue. The probe delivers light through an *optical source aperture* (e.g. a transparent window) adjacent to the array. Following illumination by

an optical pulse, the array records acoustic signals to capture a *frame* of data. In 2D imaging, each frame corresponds with a tissue slice in the probe's *imaging plane*. Figure 4.1 illustrates frames acquired at two alternating wavelengths along the probe's trajectory.

By extending equation (4.4), the opto-acoustic signals for the j -th frame are

$$y_j(\mathbf{r}_l, t) = \int_{\mathbb{R}^3} h(\mathbf{r}_l - \mathbf{r}, t) \psi_j(\mathbf{r}) \, d\mathbf{r}, \quad (4.10)$$

where $\mathbf{r}_l$ is the position of the l -th transducer element in the probe's local coordinate system, and t is time elapsed since illumination. Since the probe can move, the frame's acoustic source distribution ψ_j is defined relative to the probe's coordinates, and depends on the probe's illumination of tissue. This is equal to

$$\psi_j(\mathbf{r}) = \eta(\lambda_j, \tau_j(\mathbf{r})) \varphi(\lambda_j, \mathbf{r}), \quad (4.11)$$

where the rotation and translation for each frame are represented using an *affine transform function*

$$\tau_j(\mathbf{r}) = A_j \mathbf{r} + \mathbf{b}_j, \quad (4.12)$$

with rotation matrix A_j and translation $\mathbf{b}_j$. Thus, τ_j converts η from global coordinates to the probe's local coordinates. In global coordinates, by combining (4.2) and (4.3), η is given by

$$\eta(\lambda_j, \mathbf{r}) = \gamma(\mathbf{r}) \sum_i m_i(\lambda_j) \chi_i(\mathbf{r}), \quad (4.13)$$

where λ_j is the optical wavelength of the j -th frame. In a dual-wavelength system, λ_j sequentially alternates between two different values. Since the optical source aperture moves with the probe, the light distribution φ is assumed to remain stationary in the probe's coordinates.

4.3.2 Forward model

The forward model predicts the data received by the probe. In equations (4.10) to (4.13), the opto-acoustic signals y_j depend on: i) the volume fraction abundances χ_i , for chromophores $i = 1, \dots, n_\mu$; and, ii) the probe's orientation A_j and position $\mathbf{b}_j$, for frames $j = 1, \dots, n_f$. These parameters correspond to inputs in our forward model, but also represent the unknown variables solved during image reconstruction. The other parameters, m_i , φ and γ , are treated as constants that are determined in advance.

Volume fraction abundance of chromophores in tissue

To model the tissue, it is subdivided into voxels, arranged on a 3D grid. Each voxel is associated with a set of chromophore abundances. The total number of voxels is $n_v = n_x n_y n_z$, where n_x , n_y and n_z are the number of voxels along the x-, y- and z-axes. For the i -th chromophore, the volume fraction abundance is represented as a vector $\mathbf{x}_i \in \mathbb{R}^{n_v}$. Thus, the tissue can be represented by a matrix variable $X = [\mathbf{x}_1, \mathbf{x}_2, \dots, \mathbf{x}_{n_\mu}] \in \mathbb{R}^{n_v \times n_\mu}$, where n_μ is the number of chromophores. For convenience, this is vectorized to $\mathbf{x} = \text{vec}(X) \in \mathbb{R}^{n_v n_\mu}$.

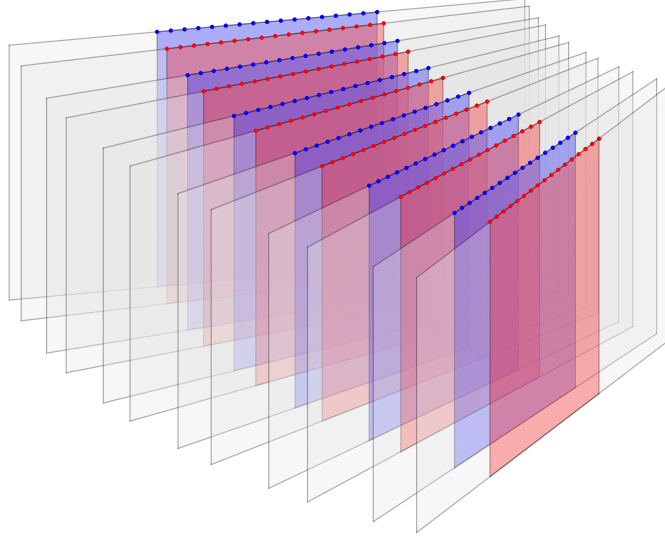


Figure 4.1: Illustration of (dual-wavelength) multi-frame acquisition. Frames at alternating optical wavelengths λ_1 (red) and λ_2 (blue) are acquired as linear array transducer follows a trajectory at the surface of a subject's tissue (not shown). Transducer elements are shown as dots at the tissue surface.

System matrix

For a tissue represented by $\mathbf{x} \in \mathbb{R}^{n_v n_\mu}$, the predicted opto-acoustic signals for the j -th frame are represented by a vector $\tilde{\mathbf{y}}_j \in \mathbb{R}^{n_m}$. The number of measurements n_m is equal to the number of transducer channels n_c times the number of samples per channel n_s . For each frame, a *system matrix* $H_j \in \mathbb{R}^{(n_m) \times (n_v n_\mu)}$ is used to represent the linear discretized operator corresponding to equation (4.10). Thus, the predicted response is

$$\tilde{\mathbf{y}}_j = H_j \mathbf{x}.$$

In our model, the operator H_j , which is composed of four components, is defined as

$$H_j = H_0 \Phi_{\lambda_j} T_{\mathbf{p}_j} M_{\lambda_j}, \quad (4.14)$$

where $M_{\lambda_j} \in \mathbb{R}^{(n_v) \times (n_v n_\mu)}$ is the *absorption matrix* for wavelength λ_j , which contains optical absorption coefficients of each chromophore; $T_{\mathbf{p}_j} \in \mathbb{R}^{n_v \times n_v}$ is the *transformation matrix* for the configuration vector $\mathbf{p}_j \in \mathbb{R}^{n_p}$, which describes probe position and orientation; $\Phi_{\lambda_j} \in \mathbb{R}^{n_v \times n_v}$ is the *optical illumination matrix* for wavelength λ_j , describing the radiant fluence distribution; and, $H_0 \in \mathbb{R}^{n_m \times n_v}$ is the *acoustic response matrix*. These are described below.

To compute signals from multiple frames, the *overall system matrix* $H \in \mathbb{R}^{(n_m n_f) \times (n_v n_\mu)}$ is given by

$$H = \begin{bmatrix} H_1 \\ H_2 \\ \vdots \\ H_{n_f} \end{bmatrix}. \quad (4.15)$$

Thus, we can write

$$\tilde{\mathbf{y}} = H\mathbf{x}, \quad (4.16)$$

where $\tilde{Y} = [\tilde{\mathbf{y}}_1, \tilde{\mathbf{y}}_2, \dots, \tilde{\mathbf{y}}_{n_f}] \in \mathbb{R}^{n_m \times n_f}$ and $\tilde{\mathbf{y}} = \text{vec}(\tilde{Y})$.

Absorption matrix (M_{λ_j})

To derive M_{λ_j} , equation (4.13) is used. It is assumed that each chromophore index $i \in \{1, \dots, n_\mu\}$ has a known absorption coefficient $m_i(\lambda_j)$ at the wavelength index $\lambda_j \in \{1, \dots, n_\lambda\}$. We define the *optical absorption vector* $\mathbf{m}_{\lambda_j} \in \mathbb{R}^{n_\mu}$ at wavelength λ_j as

$$\mathbf{m}_{\lambda_j} = [m_1(\lambda_j), m_2(\lambda_j), \dots, m_{n_\mu}(\lambda_j)]^T. \quad (4.17)$$

Next, by applying equation (4.13) in matrix form, the abundance matrix $X \in \mathbb{R}^{n_v \times n_\mu}$ can be used to find the opto-acoustic conversion efficiency by computing

$$\Gamma X \mathbf{m}_{\lambda_j}. \quad (4.18)$$

Here, $\Gamma \in \mathbb{R}^{n_v \times n_v}$ is a diagonal matrix, representing the Grüneisen parameter $\gamma(\mathbf{r})$, which applies pointwise multiplication to each voxel. To reorder equation (4.18), we use the vectorization identity, $\text{vec}(UV) = (V^T \otimes I_k) \text{vec}(U)$, which is valid for any matrices $U \in \mathbb{R}^{k \times l}$ and $V \in \mathbb{R}^{l \times m}$, where I_k represents the size k identity matrix and $\otimes$ is a Kronecker tensor product. This yields $\Gamma X \mathbf{m}_{\lambda_j} = \Gamma (\mathbf{m}_{\lambda_j}^T \otimes I_{n_v}) \text{vec}(X)$. Accordingly, we can write (4.18) as a matrix operator that is applied to $\mathbf{x} = \text{vec}(X)$. Also, for simplicity, we assume that $\gamma(\mathbf{r})$ does not vary spatially, and is represented by a constant γ_0 , such that $\Gamma = \gamma_0 I_{n_v}$. Therefore, the optical absorption matrix for (4.14) is given by

$$M_{\lambda_j} = \tilde{\mathbf{m}}_{\lambda_j}^T \otimes I_{n_v}, \quad (4.19)$$

where $\tilde{\mathbf{m}}_{\lambda_j} = \gamma_0 \mathbf{m}_{\lambda_j}$. This has a simple interpretation, which is that equation (4.19) replicates $\mathbf{m}_{\lambda_j}$ for each voxel and multiplies by γ_0 .

Transformation matrix ($T_{\mathbf{p}_j}$)

In each frame, the probe has a different position and orientation. The rotation matrix $A_j \in \mathbb{R}^{3 \times 3}$ and the translation $\mathbf{b}_j \in \mathbb{R}^3$ of equation (4.12) can be generated by a list of parameters $\mathbf{p}_j \in \mathbb{R}^{n_p}$ called the *configuration*. There is some flexibility in how A_j and $\mathbf{b}_j$ are generated from the configuration, depending on the permitted probe motions. The number of parameters n_p is equal to the degrees of freedom. We use the configuration $\mathbf{p}_j = (\boldsymbol{\theta}_j, \mathbf{b}_j)$, which has six parameters: the

three translations for $\mathbf{b}_j$, and three Euler angles $\theta_j \in \mathbb{R}^3$ to represent roll, pitch and yaw. The rotation matrix is

$$A_j = R_1(\theta_{j,1}) R_2(\theta_{j,2}) R_3(\theta_{j,3}), \quad (4.20)$$

where R_1 , R_2 and R_3 represent rotations about the three coordinate axes. If fewer degrees of freedom are required, then any of the configuration parameters can be replaced with constants to constrain the trajectory.

In earlier work [27], we described probe orientation A_j and position $\mathbf{b}_j$, and the conversion between different coordinates. Here, we define the transformation matrix $T_{\mathbf{p}_j} \in \mathbb{R}^{n_v \times n_v}$ for (4.14) as an operator that transforms voxels in $\mathbb{R}^{n_v}$ according to the configuration $\mathbf{p}_j$. In other words, $T_{\mathbf{p}_j}$ applies A_j and $\mathbf{b}_j$ to each voxel in an image. This (inversely) rotates and translates the tissue so it is situated in the local coordinate frame of the probe. In practice, the matrix $T_{\mathbf{p}_j}$ can be implemented efficiently using a custom function on a CPU or GPU.

Optical illumination matrix (Φ_{λ_j})

In the model, light is delivered by an optical aperture that remains stationary in the probe's local coordinates. Thus, for wavelength λ_j , it is assumed that the fluence profile ψ remains fixed relative to the probe. Consequently, the optical illumination matrix $\Phi_{\lambda_j} \in \mathbb{R}^{n_v \times n_v}$ applies a diagonal weighting, and corresponds to pointwise multiplication of each voxel, according to equation (4.1). Thus, $\Phi_{\lambda_j} = \text{diag}(\boldsymbol{\varphi}_{\lambda_j})$, where $\boldsymbol{\varphi}_{\lambda_j} \in \mathbb{R}^{n_v}$ is a vector representing the fluence. As described in our earlier work [27], by using a fixed fluence profile relative to the probe, Φ can be pre-computed once per wavelength, rather than solving it at each probe position. The fluence profile is governed by the radiation transport equation. It can be determined in several ways, including diffusion approximations [58]–[61], finite-element models [62], or Monte Carlo based methods [63], [64].

Acoustic response matrix (H_0)

The acoustic response matrix $H_0 \in \mathbb{R}^{n_m \times n_v}$ implements equation (4.5) in linear discretized form, as described in the next section.

4.3.3 Separable operator for linear array

In earlier work [27], we proved that a mathematical operator corresponding to equations (4.10) to (4.12) is separable. For each transducer, this implements the spherical volume integration of equations (4.4) to (4.6) to model acoustic wave propagation in a more efficient manner. By generalizing this to matrix form, the acoustic response matrix $H_0 \in \mathbb{R}^{n_m \times n_v}$ can be represented as

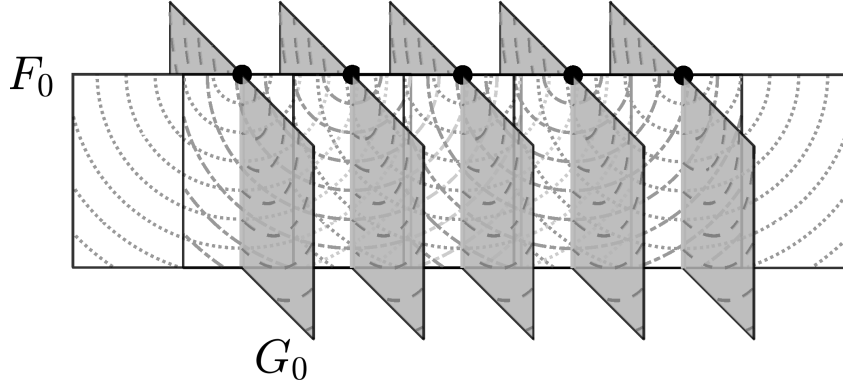


Figure 4.2: Separable acoustic response matrix [27]. To improve computational efficiency for a linear array, the response matrix $H_0 = F_0 G_0$ performs spherical volume integration of equation (4.5) in two stages. To model time-domain signals for all transducer elements (black dots), the matrix factor F_0 integrates along arcs that span a 2D plane (white), corresponding to a cross-sectional slice of tissue. The slice is generated by the matrix factor G_0 , which integrates along independent perpendicular planes (gray), spanning the 3D volume. Since the transducer elements are co-linear, all signals in F_0 require the same planes from G_0 (repeated at consecutive offsets as shown), so intermediate data can be shared. Thus, by splitting H_0 into factors F_0 and G_0 , redundant computation is eliminated.

the product of two matrices. This is written*

$$H_0 = F_0 G_0. \quad (4.21)$$

Here, the matrix factor $F_0 \in \mathbb{R}^{n_m \times n_{m'}}$ acts on the probe's 2D imaging plane. The factor $G_0 \in \mathbb{R}^{n_{m'} \times n_v}$ acts along planes perpendicular to it, spanning a 3D volume. This is illustrated in Figure 4.2. In the matrices, the intermediate number of measurements $n_{m'}$ is different from n_m .

By representing (4.21) as sparse matrices, the separable form permits higher computational efficiency because H_0 is non-factorized and less sparse than F_0 and G_0 . The performance improvement for factorized sparse matrices is similar to the case for discretized analytic equations (described in our earlier work [27]) because the sparsity pattern yields the same number of operations.

We can apply separability to the overall system matrix H of equation (4.15). By substituting (4.21) into (4.14), for frame j , we have

$$H_j = F_0 \underbrace{G_0 \Phi_{\lambda_j} T_{\mathbf{p}_j} M_{\lambda_j}}_{G_j} \quad (4.22)$$

where G_j is defined as

$$G_j = G_0 \Phi_{\lambda_j} T_{\mathbf{p}_j} M_{\lambda_j}. \quad (4.23)$$

Accordingly, (4.15) can be written as

$$H = F G, \quad (4.24)$$

* The matrix equation $H_0 = F_0 G_0$ corresponds to the compositionally separable operator $\mathcal{H} = \tilde{\mathcal{G}} \circ \mathcal{G}$, which is described in [27].

where the overall separable factors F and G are

$$F = F_0 \otimes I_{n_f} = \begin{bmatrix} F_0 & 0 & \cdots & 0 \\ 0 & F_0 & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \cdots & F_0 \end{bmatrix}, \quad (4.25)$$

and

$$G = \begin{bmatrix} G_1 \\ G_2 \\ \vdots \\ G_{n_f} \end{bmatrix}. \quad (4.26)$$

Using the separable form of equation (4.24) (instead of performing a volume integration that encounters each voxel for every transducer), reduces the computational complexity of each frame from $\mathcal{O}(n^3)$ to approximately $\mathcal{O}(n^2)$, where $n^3 = n_v$ is the number of voxels in a 3D image (assuming the number of transducers $n_c \approx n$) [27]. For a 3D image with dimensions $100 \times 100 \times 100$, this represents 100 times computational savings, compared to a non-separable approach.

4.4 IMAGE RECONSTRUCTION AND MOTION TRACKING

4.4.1 Image Reconstruction

Image reconstruction using the separable operator described in Section 4.3.3 is performed by substituting (4.15) into (4.9) to obtain the convex optimization problem

$$\begin{aligned} & \underset{\mathbf{x}}{\text{minimize}} && \|FG\mathbf{x} - \mathbf{y}\|_2^2 + \vartheta(\mathbf{x}) \\ & \text{subject to} && \mathbf{x} \in \mathcal{C} \end{aligned} \quad (4.27)$$

Here $\mathbf{x}$ represents the volume fraction abundances of the tissue chromophores, which have non-negative values. Accordingly, our implementation specifies $\mathcal{C}$ with $\mathbf{x} \geq 0$. To solve (4.27), we use a minimization algorithm [50], [52] that requires a proximal operator of the indicator function $\mathcal{I}_{\mathcal{C}}$ to confine $\mathbf{x}$ to $\mathcal{C}$. This corresponds to a simple replacement of negative values with zero after each iteration. If desired, additional constraints can be used, such as ensuring the volume fractions sum to less than one, consistent with physical principles. An overview of constraints used in optimization-based spectral unmixing is provided by Chouzenoux et al. [65].

When solving (4.27), we used a regularization function ϑ that included isotropic TV as well as ℓ_1 -minimization. Our implementation specified

$$\vartheta(\mathbf{x}) = \alpha_1 \|\mathbf{x}\|_1 + \alpha_2 \sum_{i=1}^{n_\mu} \|D\mathbf{x}_i\|_{2,1}, \quad (4.28)$$

*Algorithm 4.1: two-stage iterative 3D opto-acoustic image reconstruction***Input:** $\mathbf{y} = (\mathbf{y}_1, \dots, \mathbf{y}_{n_f}) \in \mathbb{R}^{n_f n_m}$ **Output:** $\mathbf{x} \in \mathbb{R}^{n_v n_\mu}$ **Require:** $F_0 \in \mathbb{R}^{n_m \times m'}$, $G = (G_1, \dots, G_{n_f}) \in \mathbb{R}^{n_f n_m' \times n_v n_\mu}$, $\vartheta : \mathbb{R}^{n_v n_\mu} \rightarrow \mathbb{R}$, $\rho \in \mathbb{R}^+$

```

1: function TWOSTAGERECONSTRUCT( $\mathbf{y}_1, \dots, \mathbf{y}_{n_f}$ )
2:    $\mathbf{x}^{(0)} \leftarrow 0, \mathbf{u}^{(0)} \leftarrow 0$  ▷ initialize  $\mathbf{x}$  and  $\mathbf{u}$ 
3:   for  $n = 0 \dots n_{\max} - 1$  do
4:     for  $j = 1 \dots n_f$  do
5:        $\mathbf{z}_j^{(n+1)} \leftarrow \text{RECONSTRUCT2D}(\mathbf{y}_j, G_j \mathbf{x}^{(n)} + \mathbf{u}_j^{(n)})$  ▷ 2D reconstruction for each slice
6:     end for
7:      $\mathbf{z}^{(n+1)} \leftarrow (\mathbf{z}_1^{(n+1)}, \mathbf{z}_2^{(n+1)}, \dots, \mathbf{z}_{n_f}^{(n+1)})$ 
8:      $\mathbf{x}^{(n+1)} \leftarrow \text{RECONSTRUCT3D}(\mathbf{z}^{(n+1)} - \mathbf{u}^{(n)})$  ▷ reconstruct 3D volume using all slices
9:     for  $j = 1 \dots n_f$  do
10:       $\mathbf{u}_j^{(n+1)} \leftarrow \mathbf{u}_j^{(n)} + (G_j \mathbf{x}^{(n+1)} - \mathbf{z}_j^{(n+1)})$  ▷ update dual variables
11:    end for
12:     $\mathbf{u}^{(n+1)} \leftarrow (\mathbf{u}_1^{(n+1)}, \mathbf{u}_2^{(n+1)}, \dots, \mathbf{u}_{n_f}^{(n+1)})$ 
13:  end for
14:  return  $\mathbf{x}^{(n+1)}$ 
15: end function

16: function RECONSTRUCT2D( $\mathbf{y}_0, \mathbf{u}_0$ )
17:  return  $\arg \min_{\mathbf{z}_0} \left\{ \|F_0 \mathbf{z}_0 - \mathbf{y}_0\|_2^2 + \frac{\rho}{2} \|\mathbf{u}_0 - \mathbf{z}_0\|_2^2 \right\}$ 
18: end function

19: function RECONSTRUCT3D( $\tilde{\mathbf{z}}$ )
20:  return  $\arg \min_{\mathbf{x}} \left\{ \frac{\rho}{2} \|G\mathbf{x} - \tilde{\mathbf{z}}\|_2^2 + \vartheta(\mathbf{x}) \right\}$  ▷ 3D volumetric reconstruction of chromophores
21: end function

```

where α_1 and α_2 are regularization parameters, and $D = (D_x, D_y, D_z) \in \mathbb{R}^{(3 \times n_v) \times n_v}$ is a linear matrix operator for TV regularization that computes spatial gradients in the x , y and z directions. Here, D is applied to each chromophore $\mathbf{x}_i$. In equation (4.28), the $\|\cdot\|_{2,1}$ group-norm has a dual-proximal operator that facilitates using isotropic TV with 3D volumes. Minimizing this type of equation can be performed efficiently with dual-proximal methods, such as TFOCS [50], [54] (as described in Appendix A), or by using similar approaches involving primal-dual optimization [53]. If desired, anisotropic TV can be implemented by using the ℓ_1 -norm $\|\cdot\|_1$ in (4.28) instead of $\|\cdot\|_{2,1}$, which may reduce visual performance, but is computationally simpler.

4.4.2 Two-stage iterative 3D opto-acoustic image reconstruction

To improve computation of equation (4.27), a two-stage iterative 3D reconstruction is proposed, where separable parts are solved independently. The sequence, which is performed iteratively, involves first reconstructing a monochrome (single-wavelength) 2D slice for each frame, followed by 3D volumetric reconstruction of chromophores.

Algorithm 4.2: opto-acoustic image reconstruction with motion tracking

Input: $\mathbf{y} = (\mathbf{y}_1, \dots, \mathbf{y}_{n_f}) \in \mathbb{R}^{n_f n_m}$

Output: $\mathbf{x} \in \mathbb{R}^{n_v n_\mu}$, $\mathbf{p} \in \mathbb{R}^{n_p n_f}$

```

1: procedure RECONSTRUCTIONANDTRACKING( $\mathbf{y}$ )
2:    $\mathbf{x}^{(0)} \leftarrow 0$ ,  $\mathbf{p}^{(0)} \leftarrow 0$  ▷ initialize  $\mathbf{x}$  and  $\mathbf{p}$ 
3:   for  $k = 0 \dots k_{\max} - 1$  do
4:     for  $j = 1 \dots n_f$  do
5:        $H_{\mathbf{p}_j}^{(k)} \leftarrow H_0 \Phi_{\lambda_j} T_{\mathbf{p}_j}^{(k)} M_{\lambda_j}$  ▷ update the system response of frame  $j$  from (4.14)
6:        $J_{\mathbf{p}_j}^{(k)} \leftarrow \left. \frac{\partial H_{\mathbf{p}_j}^{(k)} \mathbf{x}^{(k)}}{\partial \mathbf{p}_j} \right|_{\mathbf{p}_j^{(k)}}$  ▷ update Jaccobian of frame  $j$ 
7:     end for
8:      $(\mathbf{x}^{(k+1)}, \Delta \mathbf{p}^{(k+1)}) \leftarrow \arg \min_{(\mathbf{x}, \Delta \mathbf{p}) \in \mathcal{C}_k} \left\{ \left\| H_{\mathbf{p}}^{(k)} \mathbf{x} + J_{\mathbf{p}}^{(k)} \Delta \mathbf{p} - \mathbf{y} \right\|_2^2 + \vartheta(\mathbf{x}) \right\}$  ▷ solve (4.34a)
9:      $\mathbf{p}^{(k+1)} \leftarrow \mathbf{p}^{(k)} + \Delta \mathbf{p}^{(k+1)}$  ▷ update  $\mathbf{p}$  from (4.34b)
10:  end for
11: end procedure
    
```

Using the separable operator of Section 4.3.3, equation (4.27) is split into two parts. From (4.22) and (4.23), when H_j is applied to $\mathbf{x}$, we can write

$$H_j \mathbf{x} = F_0 \underbrace{G_j \mathbf{x}}_{\mathbf{z}_j} = F_0 \mathbf{z}_j, \quad (4.29)$$

where $\mathbf{z}_j \in \mathbb{R}^{n_{m'}}$ is a new variable, defined by

$$\mathbf{z}_j = G_j \mathbf{x}. \quad (4.30)$$

We write $Z = [\mathbf{z}_1, \dots, \mathbf{z}_{n_f}] \in \mathbb{R}^{n_{m'} \times n_f}$ and $\mathbf{z} = \text{vec}(Z)$. Thus, for the overall system matrix,

$$H\mathbf{x} = FG\mathbf{x} = F\mathbf{z}, \quad (4.31)$$

where $G\mathbf{x} = \mathbf{z}$. Using this substitution, equation (4.27) becomes

$$\begin{aligned} & \underset{\mathbf{x}, \mathbf{z}}{\text{minimize}} \quad \|F\mathbf{z} - \mathbf{y}\|_2^2 + \vartheta(\mathbf{x}) \\ & \text{subject to} \quad \mathbf{z} = G\mathbf{x}, \end{aligned} \quad (4.32)$$

where the constraint $\mathbf{x} \in \mathcal{C}$ is omitted for clarity.

Equation (4.32) can be solved with the ADMM splitting algorithm, as described in Appendix A. The result obtained by applying (4.32) to (4.A.5) is presented as Algorithm 4.1. An interesting interpretation of Algorithm 4.1 is that there is an intermediate variable $\mathbf{z}_j$ for each frame, corresponding to a monochrome 2D reconstructed image. Each reconstructed $\mathbf{z}_j$ requires no inherent positional information, since it is in the probe's local coordinates. Algorithm 1 performs an outer loop, with

two separate inner minimizations. First, the algorithm reconstructs a 2D image $\mathbf{z}_j$ for each frame. Then, once $\mathbf{z}_j$ is formed for all frames, the 3D volume $\mathbf{x}$ is reconstructed from the intermediate variables, using each frame's position and orientation. Since the positional information is not required until the second stage, motion tracking can be solved using data computed from the first stage, as described in Section 4.4.3.

4.4.3 Image Reconstruction combined with motion tracking

Motion tracking is developed from equation (4.9), using the system matrix H of equation (4.15), which depends on the configuration parameters $\mathbf{p} = (\mathbf{p}_1, \dots, \mathbf{p}_{n_f})$ that describe the probe orientation and position for each frame. To highlight the non-linear dependence of H on $\mathbf{p}$, we write the system matrix as $H \equiv H_{\mathbf{p}}$. To simultaneously perform reconstruction of $\mathbf{x}$, while determining probe configuration $\mathbf{p}$, it is desirable to solve

$$\underset{(\mathbf{x}, \mathbf{p}) \in \mathcal{C}}{\text{minimize}} \quad \|H_{\mathbf{p}} \mathbf{x} - \mathbf{y}\|_2^2 + \vartheta(\mathbf{x}) \quad (4.33)$$

However, due to the form of $H_{\mathbf{p}}$, which is non-linear in $\mathbf{p}$, equation (4.33) is not convex, which makes finding a solution difficult.

To convert (4.33) to a form that can be solved, a linear approximation to $H_{\mathbf{p}}$ around an initial estimate of $\mathbf{p}$ is used. For an incremental change in configuration parameters $\Delta \mathbf{p} \in \mathbb{R}^{(n_p n_f)}$, the linear approximation is

$$H_{(\mathbf{p} + \Delta \mathbf{p})} \approx H_{\mathbf{p}} + J_{\mathbf{p}} \Delta \mathbf{p},$$

where $J_{\mathbf{p}} = \frac{\partial}{\partial \mathbf{p}}(H_{\mathbf{p}} \mathbf{x}) \in \mathbb{R}^{n_m \times (n_p n_f)}$ represents the Jaccobian derivative of $H_{\mathbf{p}}$ at $\mathbf{x}$ with respect to each parameter in $\mathbf{p}$. This permits iteratively solving a relaxed approximation to (4.33), where each iteration is a two step process. This two step approach is known as sequential convex optimization. At the k -th iteration, first, solutions for $\mathbf{x}^{(k+1)}$ and $\Delta \mathbf{p}^{(k+1)}$ are simultaneously solved. Then, $\mathbf{p}^{(k+1)}$ is solved by incrementally updating $\mathbf{p}^{(k)}$ with $\Delta \mathbf{p}^{(k+1)}$. Thus, each iteration consists of the following two steps:

Step 1:

$$\begin{bmatrix} \mathbf{x}^{(k+1)} \\ \Delta \mathbf{p}^{(k+1)} \end{bmatrix} = \arg \min_{(\mathbf{x}, \Delta \mathbf{p}) \in \mathcal{C}_k} \left\{ \|H_{\mathbf{p}}^{(k)} \mathbf{x} + J_{\mathbf{p}}^{(k)} \Delta \mathbf{p} - \mathbf{y}\|_2^2 + \vartheta(\mathbf{x}) \right\} \quad (4.34a)$$

Step 2:

$$\mathbf{p}^{(k+1)} = \mathbf{p}^{(k)} + \Delta \mathbf{p}^{(k+1)} \quad (4.34b)$$

This is illustrated in Algorithm 4.2.

To constrain for constant velocity motion estimation, $\mathcal{C}_k$ can project $\mathbf{p}^{(k)}$ onto a linear trajectory along the probe's elevational axis after each iteration using robust fitting.

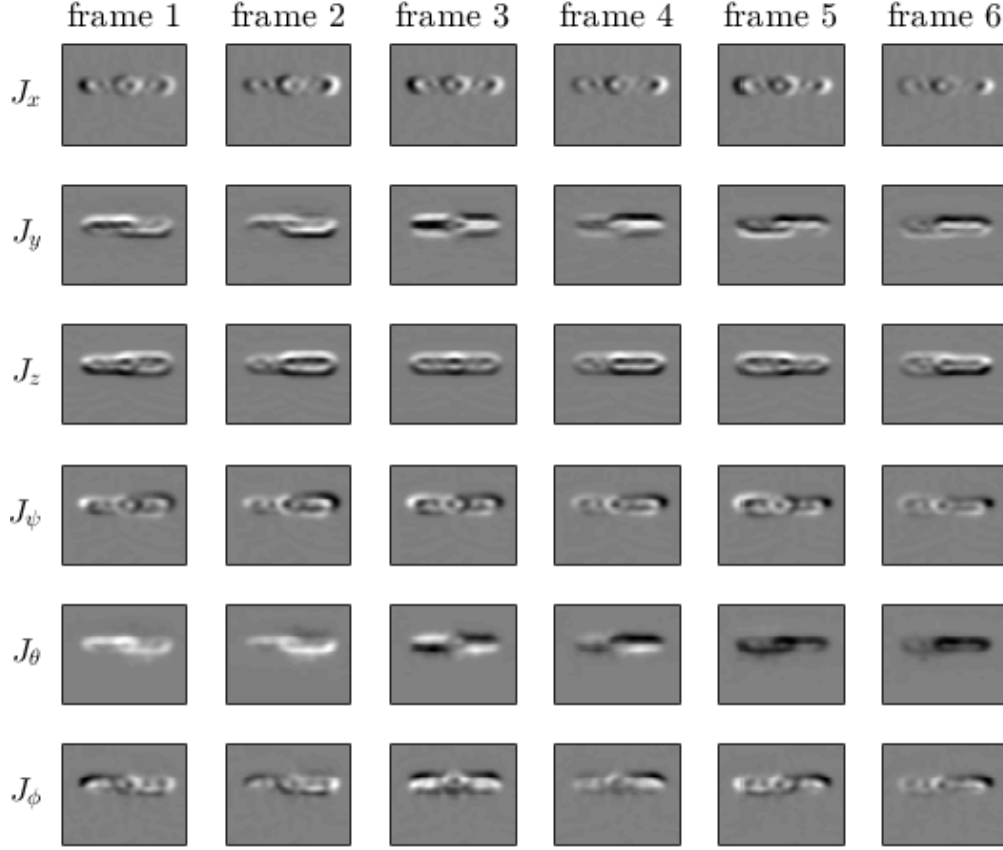


Figure 4.3: Jacobian matrices for 6 acquired frames of digital phantom. The differences J_x , J_y , J_z , J_ψ , J_θ , and J_ϕ correspond to unit changes in $\mathbf{z}$ due to x , y and z axis translations, and roll, pitch and yaw rotations.

4.4.4 Efficient implementation of reconstruction and tracking

By combining separability of Section 4.3.3 with Algorithm 4.2, additional advantages can be achieved. For example, when a 2D slice is separately reconstructed using data from each frame, this can be used to determine an initial estimate of motion along the lateral axis of the probe. We modify equation (4.32) into a split form similar to equation (4.34a). The split form permits applying the Jacobian matrix J_p in the 2D image-domain of $\mathbf{z}$, rather than in the time-domain of measurement data $\mathbf{y}$, which leads to a more efficient implementation. With these modifications, our implementation of Step 1 becomes

$$\begin{aligned}
 & \underset{\mathbf{x}, \mathbf{z}, \Delta \mathbf{p}}{\text{minimize}} && \|F\mathbf{z} - \mathbf{y}\|_2^2 + \vartheta(\mathbf{x}) \\
 & \text{subject to} && \mathbf{z} = G_{\mathbf{p}}^{(k)} \mathbf{x} + J_{\mathbf{p}}^{(k)} \Delta \mathbf{p}, \\
 & && \mathbf{x} \geq 0,
 \end{aligned} \tag{4.35}$$

where $\vartheta(\mathbf{x})$ is the same as equation (4.28).

As described in Appendix A, the TFOCS algorithm performs minimization using first-order iterations with an accelerated proximal gradient (APG) method [50], [66]. The approach can handle convex optimization problems in *block-composite form* (BCF), which is described in equation (4.A.6). However, to solve a problem in BCF form, it is manually converted to its dual form, described in equation (4.A.7). To represent equation (4.35) in BCF form, we use a primal variable $\mathbf{v} = (\mathbf{z}, \mathbf{x}, \Delta \mathbf{p})$. The result is illustrated in Algorithm 4.3, which combines Algorithm 4.1 with Algorithm 4.2. At the k -th (outer) iteration, the block-composite system matrix $L^{(k)}$ is

$$L^{(k)} = \begin{bmatrix} -1 & G_{\mathbf{p}}^{(k)} & J_{\mathbf{p}}^{(k)} \\ F & 0 & 0 \\ D & 0 & 0 \\ 1 & 0 & 0 \end{bmatrix}, \quad (4.36)$$

where D is the linear operator for TV regularization, as used in equation (4.28). The offset constant for (4.A.6) is $\mathbf{c} = (0, \mathbf{y}, 0, 0)$. To encode (4.35), the function map $\xi = [\mathcal{I}_0, \|\cdot\|_2, \|\cdot\|_{2,1}, \|\cdot\|_1]$ is used, which implements $\vartheta(\mathbf{x})$ and $\mathcal{I}_0$ encodes the equality constraint. The positivity constraint is encoded by ξ_0 . The proximal operator $\text{prox}_{\xi_0}(\mathbf{v})$ and dual-proximal operator $\text{prox}_{\xi^*}(\mathbf{u})$, which are required in equation (4.A.7), are

$$\text{prox}_{\xi_0} = \begin{bmatrix} \text{prox}_{\mathcal{I}_{\mathbb{R}_+^n}} \\ \text{prox}_{\mathcal{I}_{\mathbb{R}^n}} \\ \text{prox}_{\mathcal{I}_{\mathbb{R}^n}} \end{bmatrix}, \quad \text{prox}_{\xi^*} = \begin{bmatrix} \text{prox}_{\ell_2} \\ \text{prox}_{\mathcal{I}_{\mathbb{R}^n}} \\ \text{prox}_{\ell_{2,\infty}}(\alpha_2) \\ \text{prox}_{\ell_{\infty}}(\alpha_1) \end{bmatrix}. \quad (4.37)$$

Here, the function $\text{prox}_{\mathcal{I}_{\mathbb{R}_+^n}}$ represents projection into the positive halfspace $\mathbb{R}_+^n$, which implements the constraint $\mathbf{x} \geq 0$, replacing negative values with zero. The unconstrained primal constraints are represented by projection into $\mathbb{R}^n$ using $\text{prox}_{\mathcal{I}_{\mathbb{R}^n}}$. For prox_{ξ^*} , the remaining terms in equation (4.35) are converted to dual form. The ℓ_2 -norm $\|\cdot\|_2$ is self-dual, so its dual-proximal operator is prox_{ℓ_2} . Implementing the ℓ_1 minimization term in $\vartheta(\mathbf{x})$ involves its dual, $\text{prox}_{\ell_{\infty}}$. The dual for the $\|\cdot\|_{2,1}$ group-norm in (4.28) is $\text{prox}_{\ell_{2,\infty}}$. The constants α_1 and α_2 correspond to the regularization parameters in (4.28).

In Algorithm 3, at iteration k , the Jacobian matrix $J_{\mathbf{p}}^{(k)}$ can be computed by finite difference with respect to changes in $\mathbf{p}^{(k)}$. For illustration, Figure 4.3 shows $J_{\mathbf{p}}$, computed in the 2D image domain of $\mathbf{z}$, obtained from a digital phantom (described in Section 4.5.1) using 6 frames. When solving equation (4.35), since the image $\mathbf{x}$ is initially unknown, $J_{\mathbf{p}}^{(0)}$ is initialized to zero and updated each iteration.

Algorithm 4.3: Alternate implementation of image reconstruction with motion tracking

Input: $\mathbf{y} = (\mathbf{y}_1, \dots, \mathbf{y}_{n_f}) \in \mathbb{R}^{n_f n_m}$

Output: $\mathbf{x} \in \mathbb{R}^{n_v n_\mu}, \mathbf{p} \in \mathbb{R}^{n_f n_p}$

```

1: procedure RECONSTRUCTIONANDTRACKING( $\mathbf{y}$ )
2:    $\mathbf{z}^{(0)} \leftarrow 0, \mathbf{x}^{(0)} \leftarrow 0, \mathbf{p}^{(0)} \leftarrow 0$  ▷ initialize  $\mathbf{z}, \mathbf{x}$  and  $\mathbf{p}$ 
3:    $\xi \leftarrow [\mathcal{I}_0 \quad \|\cdot\|_2 \quad \|\cdot\|_{2,1} \quad \|\cdot\|_1]$ 
4:   for  $k = 0 \dots k_{\max} - 1$  do
5:     
$$\begin{bmatrix} \mathbf{z}^{(k+1)} \\ \mathbf{x}^{(k+1)} \\ \Delta \mathbf{p}^{(k+1)} \end{bmatrix} \leftarrow \arg \min_{(\mathbf{z}, \mathbf{x}, \Delta \mathbf{p}) \in \mathcal{C}_k} \left\{ \xi \left( \begin{bmatrix} -1 & G_{\mathbf{p}}^{(k)} & J_{\mathbf{p}}^{(k)} \\ F & 0 & 0 \\ D & 0 & 0 \\ 1 & 0 & 0 \end{bmatrix} \begin{bmatrix} \mathbf{z} \\ \mathbf{x} \\ \Delta \mathbf{p} \end{bmatrix} - \begin{bmatrix} 0 \\ \mathbf{y} \\ 0 \\ 0 \end{bmatrix} \right) \right\}$$
 ▷ solve Eq. (4.35)
6:      $\mathbf{p}^{(k+1)} \leftarrow \mathbf{p}^{(k)} + \Delta \mathbf{p}^{(k+1)}$  ▷ update trajectory
7:   end for
8: end procedure

```

4.5 RESULTS AND IMPLEMENTATION

4.5.1 3D reconstruction of digital phantom

In this section, 3D multi-chromophore reconstruction is demonstrated using the digital phantom shown in Figure 4.4. To model different chromophores, the phantom contains inclusions consisting of oxy-hemoglobin (HbO₂) and deoxy-hemoglobin (HHb). The phantom's geometry is intended to be suggestive of a tumor, with a network of arteries and veins. Two spheres and two links (ring shapes) of each chromophore are arranged symmetrically, as shown. The spheres have diameter 2mm and are centered at depth 15mm. The links are rotated $\pm 45^\circ$ about the z-axis, have a 2mm ring-diameter, a major-axis length of 18mm, and are centered at depth 15mm.

Acquisition was modeled for a 2D OA probe with linear-array transducer. The illumination φ was pre-computed by assuming two rectangular optical apertures adjacent to the probe, with an effective optical attenuation for tissue of $\mu_{\text{eff}} = 1.2\text{cm}^{-1}$ at each wavelength. As shown in Figure 4.4, the probe follows a curved trajectory to acquire frames. Alternating 757nm and 1064nm optical pulses were modeled using a non-uniform pulse sequence, which involved a shorter delay after the first pulse than the second pulse. This type of sequence is used in conventional 2D image formation because motion artifacts are minimized by rapid acquisition of successive wavelengths, and the pulse repetition rate is limited by safety. Thus, our model includes frame positions that depend on probe trajectory as well as pulse timing.

The phantom was simulated with a 3D volume of $256 \times 256 \times 128$ voxels for each chromophore, with grid spacing 0.23mm/voxel. Transducer elements were modeled using a line-aperture for f_a with 4mm elevational width, cosine directionality α , and ideal electro-mechanical response β , per equation (4.5). A dataset of acoustic signals with added white noise was generated for 14 OA frames, as shown in Figure 4.4.

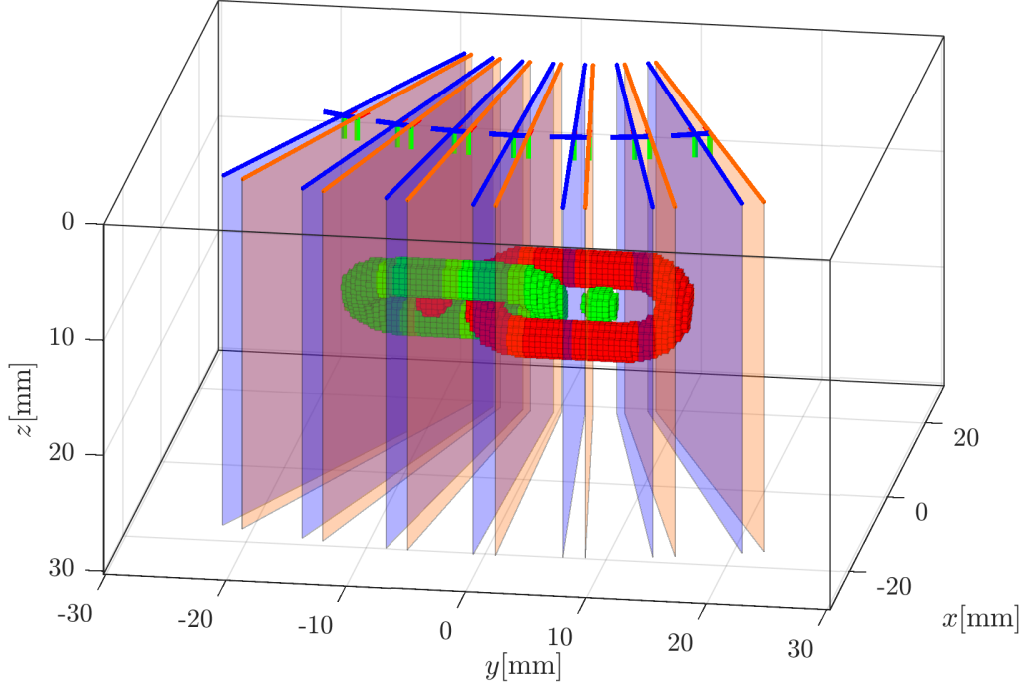


Figure 4.4: A 3D digital phantom with chromophores oxy-hemoglobin (green) and deoxy-hemoglobin (red). The phantom contains two spheres and two links, arranged symmetrically and assigned opposite chromophores. The probe moves along a curved trajectory and acquires 14 OA frames with alternating optical wavelengths (represented by blue and orange planes). Position of linear array at tissue surface corresponds to blue and orange lines.

For reconstruction, the minimization-based approach of equation (4.32) was used. The simulated dataset, along with probe position and orientation, served as input. The multi-chromophore reconstructed volume $X = [x_1, x_2]$ consisted of $(128 \times 128 \times 64) \times 2$ voxels, with grid spacing 0.3mm/voxel, which is different from the simulated grid. A volume rendering of the reconstruction is shown in Figure 4.5, which displays $x_2 - x_1$ in a red/green palette to demonstrate chromophore reconstruction. Performance is considered in the next section.

4.5.2 Reconstruction and motion tracking using digital phantom

To examine our approach for reconstruction and motion tracking, the multi-chromophore digital phantom of Section 4.5.1 was used. In the simulation, the OA probe was moved at constant velocity of 15 mm/s along its elevational axis, which was aligned with the y-coordinate of the phantom. Illumination alternated between 757nm and 1064nm wavelengths. A non-uniform pulse sequence was used with a 50ms delay after the 757nm wavelength and a 150ms delay after the 1064nm wavelength. A total of 14 frames were acquired at an average frame rate of 10Hz.



Figure 4.5: 3D reconstruction of digital phantom of Figure 4.4.

Reconstruction was performed using Algorithm 3. The reconstructed volume had $(64 \times 64 \times 64) \times 2$ voxels, with grid spacing 0.6mm/voxel. The variables $\mathbf{x}^{(k)}$ and $\mathbf{p}^{(k)}$ were stored after each outer iteration k . An initial velocity estimate of 25mm/s was specified. There were 10 outer iterations performed, and each used 80 inner iterations. Reconstruction was implemented in Matlab using the TFOCS [66] solver. The system matrices F and G were computed by custom GPU functions [27] running on a GeForce GTX Titan with 3072 cores and 24GB RAM. Total processing time was 1090 seconds. The results are shown in Figure 4.6, which illustrates the evolution of $\mathbf{x}^{(k)}$ after k iterations. As $\mathbf{p}^{(k)}$ becomes more accurate, the reconstructed 3D image improves. In the Supplemental Materials, Figure 4.S.1 displays cross-sections of the volume as the reconstruction converges. The convergence of the normalized error of $\mathbf{x}^{(k)}$ and $\mathbf{p}^{(k)}$, relative to ground truth, is plotted in Figure 4.S.2. Figure 4.S.3 illustrates the evolution of the each frame's y -coordinate during the reconstruction.

4.5.3 Reconstruction from clinical data

An OA dataset of a fibroadenoma (a benign breast lesion) was acquired during a clinical feasibility study involving an investigational Imagio[®] breast imaging system [3]. Using this dataset, reconstruction with the proposed technique was compared to 2D back-projection. The resulting images are shown in Figure 4.7. Mathematical optimization was performed using Algorithm 1. The system matrix H was decomposed into F and G as described in equation (4.24). An outer iteration count of $n_{\max} = 1$ was specified, using elevational velocity of 1.2mm/s. 40 frames at 757nm and 1064nm wavelengths were processed. The minimization was solved using TFOCS [66] with 400 inner iterations for F and G . Total variation and sparse L1 regularization were used for $\vartheta(\mathbf{x})$. The reconstructed volume used size $(256 \times 256 \times 128) \times 2$, with grid spacing 0.15mm/voxel, corresponding to dimensions of 38mm $\times$ 38mm $\times$ 19mm. In addition to reconstruction of individual 757nm and 1064nm wavelengths, in Figure 4.7, statistical color mapping [4], [67] was used to display regions of high and low relative blood oxygen saturation, overlaid on conventional ultrasound. Using

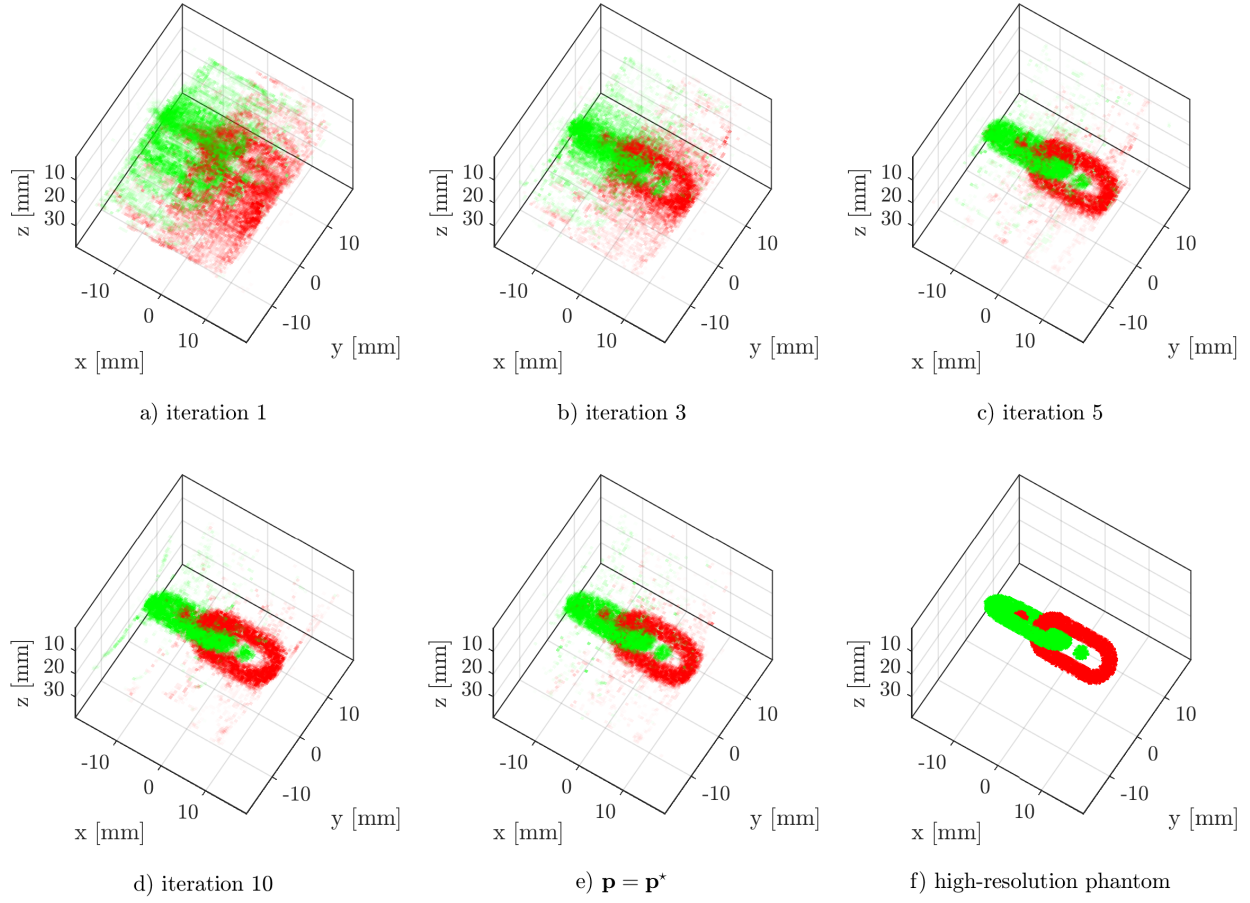


Figure 4.6: 3D reconstruction while solving elevational probe motion using Algorithm 3. The reconstructed volume $\mathbf{x}^{(k)}$ has $64 \times 64 \times 64$ voxels for each chromophore, where k represents the outer iteration count. (a) The $\mathbf{x}^{(1)}$ reconstruction, generated after 1st outer iteration, using initial position estimate $\mathbf{p}^{(0)}$. The (b) $\mathbf{x}^{(3)}$ reconstruction, (c) $\mathbf{x}^{(5)}$ reconstruction, and (d) $\mathbf{x}^{(10)}$ reconstruction. (e) Reconstruction with a single outer iteration when probe position $\mathbf{p}$ is initially set to ground truth $\mathbf{p}^*$. (f) The ground truth $\mathbf{x}^*$ used to simulate measured acoustic waves, which has a denser grid geometry of $128 \times 128 \times 128$ voxels. The y-coordinate position error for (a)-(d) is shown in Figure 4.S.3.

the optimization-based technique, the capsular vessels surrounding the lesion reconstruct with significantly reduced artifact and higher contrast compared to the backprojection-based approach. A 3D isocontour plot of the reconstructed chromophores is shown in Figure 4.8.

4.5.4 Reconstruction using biologically-equivalent phantom

Using the proposed techniques, reconstruction was performed on a biologically-equivalent phantom [4] containing vessels filled with oxygenated and deoxygenated blood. The contrast-to-background ratio (CBR) was evaluated as function of depth, and improved by a factor of ~ 20 for 3D mathematical optimization compared to 2D backprojection. Results are presented in the Supplemental Materials (Figures 4.S.4 to 4.S.9).

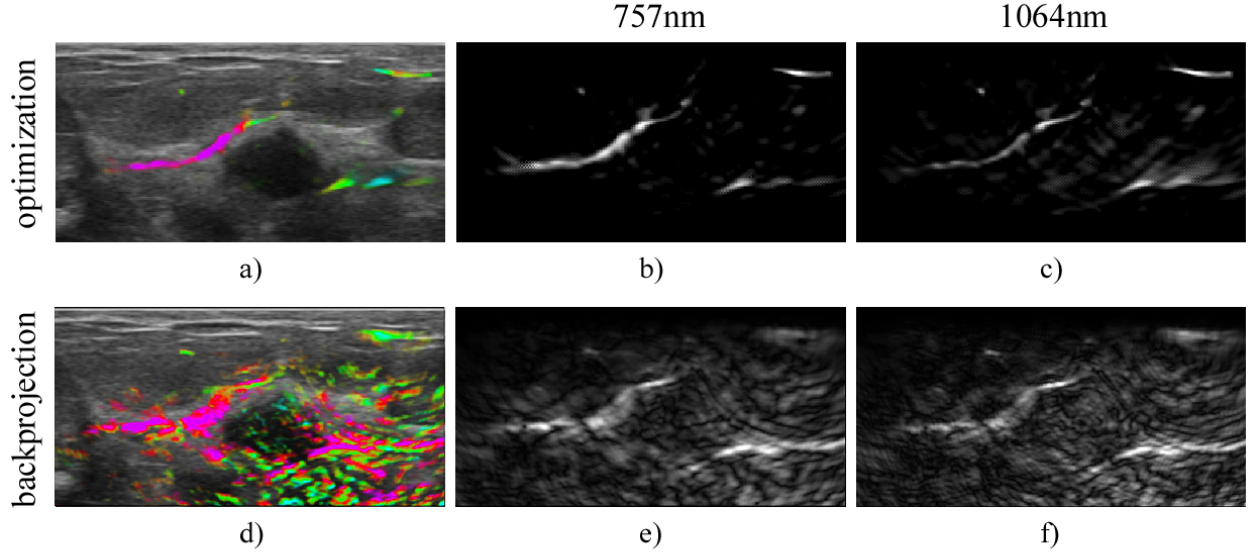


Figure 4.7: Opto-acoustic images of a benign breast lesion. Images are generated from OA measurements obtained during a clinical feasibility study [3]. Reconstruction involved (a)-(c) mathematical optimization with Algorithm 1; and, (d)-(f) formula-based backprojection. Capsular vessels that surround the lesion are visible using OA. In (a) and (d), colorized OA data is overlaid on conventional grayscale ultrasound to indicate regions of HbO₂ (green) and HHb (red). The 757nm wavelength for (b) and (e) is absorbed preferentially by HHb. The 1064nm wavelength for (c) and (f) is absorbed preferentially by HbO₂. Image dimensions are 38mm $\times$ 19mm.

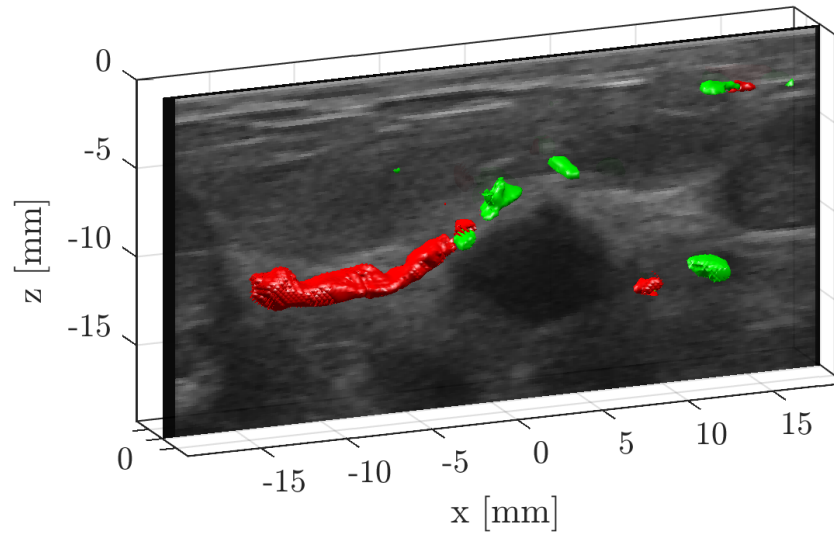


Figure 4.8: Reconstructed 3D volume of benign lesion using proposed technique. To indicate oxygenated (green) and deoxygenated (red) hemoglobin, isocontours of the 3D chromophore difference map $x_{\text{HHb}} - x_{\text{HbO}_2}$ are displayed. 2D grayscale ultrasound is shown in the plane $y = 0$. In ultrasound, the lesion appears as a dark region from 10mm to 15mm depth.

4.5.5 *Varying of frame count and transducer geometry*

To evaluate varying of frame count and transducer geometry, reconstruction was performed on a digital phantom using mathematical optimization and backprojection. Artifact suppression and peak-signal-to-noise ratio (PSNR) improved with mathematical optimization, with higher frame counts, and with matching transducer geometries. Results are presented in the Supplemental Materials (Figures 4.S.10 to 4.S.17).

4.6 DISCUSSION

In Section 4.5.1, we demonstrated multi-wavelength reconstruction using frames acquired as the probe followed a curved trajectory. This illustrates that the model described in Section 4.3 was able to reconstruct a phantom consisting of multiple chromophores.

Due to the trajectory’s radius of curvature, there was different effective spacing between frames at one side of phantom compared to the other, which can be seen in Figure 4.4. Visually, this did not lead to degradation in the reconstruction shown in Figure 4.5. However, if the spacing between frames (or curvature) were significantly increased, this would likely lead to degradation of the reconstruction. Further examination of this phenomenon is the subject of future work.

Several related motion detection and reconstruction approaches have been studied in ultrasound imaging, where motion is determined by sensors, or by computing correlations of ultrasonic speckle [30]–[38]. For several reasons, including differences in elevational resolution and speckle characteristics, these ultrasound-based approaches are not generally applicable to OA. Nevertheless, in OA, correlation-based approaches can readily track lateral (in-plane) motion along the linear array’s axis; however, elevational (out-of-plane) motion, perpendicular to the array, is more difficult to estimate, which is an advantage of our approach. Since image reconstruction and motion tracking are combined, in our approach variables representing probe motion are solved simultaneously with variables that represent image voxels. In this formulation, we find that out-of-plane OA sources can actually benefit elevational motion estimation by acting as targets to “lock onto”. The results of Section 4.5.2 demonstrate how our approach can solve elevational motion in multi-frame acquisition, without using external sensors. Results of Section 4.5.3 suggest the proposed technique could potentially lead to significant image quality improvements in systems using linear-array OA probes.

4.7 CONCLUSION

This article presented an approach to simultaneously reconstruct 3D images and solve motion for an OA probe using sequential convex optimization. The model developed in Section 4.3 was used to implement the 3D reconstruction algorithms described in Section 4.4. We demonstrated that 3D volumes with multiple chromophores could be reconstructed from 2D OA probe measurements obtained at multiple optical wavelengths. The ability to determine elevational probe velocity was demonstrated in Section 4.5.2 using a 3D digital phantom. We demonstrated improvement in CBR

and PSNR by analyzing reconstruction with phantoms (Supplemental Materials). Reconstruction of data from a clinical study (Section 4.5.3) suggested the proposed technique potentially enables significant image quality improvements in clinical settings. Future work includes additional tests involving more complex motion trajectories; determining the effect of different probe motion on reconstructed image quality to further characterize the algorithm; and, implementation for a real-time imaging system.

4.A APPENDIX

The accelerated proximal gradient method [45], [46], [50], [52] solves a convex optimization problem of the form

$$\underset{\mathbf{x}}{\text{minimize}} \quad f(\mathbf{x}) + g(\mathbf{x}) \quad (4.A.1)$$

where g is a smooth convex function (e.g. the ℓ_2 norm), and f is a non-smooth convex function (e.g. the ℓ_1 norm). This can implement an image reconstruction problem similar to equation (4.9). The solution of (4.A.1) is iteratively obtained as

$$\begin{aligned} \mathbf{x}^{k+1} &:= \text{prox}_{\rho f} \left(\mathbf{w}^k - \rho \nabla g(\mathbf{w}^k) \right) \\ \mathbf{w}^{k+1} &:= \mathbf{x}^{k+1} + \beta_k (\mathbf{x}^{k+1} - \mathbf{x}^k) \end{aligned} \quad (4.A.2)$$

where ρ is a scaling parameter, $\beta_k = \frac{k}{k+3}$, and k is the iteration count. The initial values $\mathbf{x}^0$ and $\mathbf{w}^0$ are set to zero. Since g is smooth, its gradient ∇g can be computed analytically. For the non-smooth function, the *proximal operator* of f is defined as

$$\text{prox}_{\tau f}(\mathbf{x}) = \arg \min_{\mathbf{u}} \left(f(\mathbf{u}) + \frac{1}{2\tau} \|\mathbf{u} - \mathbf{x}\|_2^2 \right) \quad (4.A.3)$$

where τ is a scaling constant. Many non-smooth functions have a proximal operator prox_f that is efficient to compute. However, when a function f is composed with linear operator G , the resulting function $f \circ G$ does not necessarily have a similarly efficient proximal operator.

To deal with such a situation, the ADMM algorithm [49], [52] solves a convex optimization problem of the form

$$\begin{aligned} \underset{\mathbf{x}, \mathbf{z}}{\text{minimize}} \quad & g(\mathbf{z}) + \vartheta(\mathbf{x}) \\ \text{subject to} \quad & \mathbf{z} = G\mathbf{x} \end{aligned} \quad (4.A.4)$$

Here, the variables $\mathbf{x}$ and $\mathbf{z}$ are both minimized. The solution to (4.A.4) is achieved by iteratively computing

$$\begin{aligned} \mathbf{z}^{k+1} &:= \arg \min_{\mathbf{z}} \left(g(\mathbf{z}) + \frac{\rho}{2} \|\mathbf{z} - G\mathbf{x}^k - \mathbf{u}^k\|_2^2 \right) \\ \mathbf{x}^{k+1} &:= \arg \min_{\mathbf{x}} \left(\vartheta(\mathbf{x}) + \frac{\rho}{2} \|G\mathbf{x} - \mathbf{z}^{k+1} + \mathbf{u}^k\|_2^2 \right) \\ \mathbf{u}^{k+1} &:= \mathbf{u}^k + G\mathbf{x}^{k+1} - \mathbf{z}^{k+1} \end{aligned} \quad (4.A.5)$$

where $\mathbf{u}$ is a dual-update variable, and ρ is a scaling parameter. In Section 4.4, equation (4.A.5) is used to derive an algorithm for 3D reconstruction.

The TFOCS solver [54], [66] can handle a convex optimization problem in block composite form (BCF), represented as

$$\underset{\mathbf{v}}{\text{minimize}} \quad \zeta_0(\mathbf{v}) + \sum_{i=1}^m \zeta_i(L_i \mathbf{v} - \mathbf{c}_i) \quad (4.A.6)$$

where

$$L = \begin{bmatrix} L_1 \\ \vdots \\ L_m \end{bmatrix}, \quad \mathbf{c} = \begin{bmatrix} \mathbf{c}_1 \\ \vdots \\ \mathbf{c}_m \end{bmatrix}$$

Here, L is a block matrix containing m linear operator matrices L_i , and $\mathbf{c}_i$ is an offset vector. The smooth function ζ_0 is applied to the composite vector $\mathbf{v}$, and the functions ζ_i , $i = 1 \dots m$ are applied to the domain $L_i \mathbf{v} - \mathbf{c}_i$. For convenience, in (4.A.6) the summation $\sum_{i=1}^m \zeta_i(L_i \mathbf{v} - \mathbf{c}_i)$ can be written $\zeta(L\mathbf{v} - \mathbf{c})$, where $\zeta = [\zeta_1, \dots, \zeta_m]$ is a function map. The TFOCS solver, rather than solving equation (4.A.6) directly, minimizes a dual optimization problem of the form

$$\underset{\mathbf{u}}{\text{minimize}} \quad \zeta_0^* \left(\sum_{i=1}^m L_i^T \mathbf{u}_i \right) + \sum_{i=1}^m \zeta_i^*(-\mathbf{u}_i + \mathbf{c}_i) \quad (4.A.7)$$

where $\zeta_0^*(\mathbf{v})$ is the dual conjugate of $\zeta_0(\mathbf{v})$ and $\zeta_i^*(\mathbf{u})$ is the dual conjugate of $\zeta_i(\mathbf{v})$ [54], [66]. This computation is more efficient because the linear operator matrices L_i are moved from the non-smooth functions ζ_i in (4.A.6) to the smooth function ζ_0^* in (4.A.7). In this case, solving (4.A.7) with (4.A.2) requires the smooth-function gradient $\nabla \zeta_0^* = \text{prox}_{\zeta_0}$ and the dual-proximal operator prox_{ζ^*} , which can be obtained from prox_{ζ} using a mathematical identity [45], [54]. Accordingly, the solution of (4.A.7) is computed iteratively as

$$\begin{aligned} \mathbf{v}^{k+1} &:= \text{prox}_{\tau \zeta_0}(\mathbf{v}^{k-\alpha_k} + \tau L^T \mathbf{w}^k) \\ \mathbf{u}^{k+1} &:= \mathbf{c} - \text{prox}_{\sigma \zeta^*}(\mathbf{c} - \mathbf{w}^k + \sigma L \mathbf{v}^{k+1}) \\ \mathbf{w}^{k+1} &:= \mathbf{u}^{k+1} + \beta_k(\mathbf{u}^{k+1} - \mathbf{u}^k) \end{aligned} \quad (4.A.8)$$

where $\beta_k = \frac{k}{k+3}$, $\alpha_k = k - a \left\lfloor \frac{k}{a} \right\rfloor$, with $a \in \mathbb{Z}^+$, and σ and τ are scaling parameters.

4.S SUPPLEMENTAL MATERIAL

4.S.1 Convergence

In this section, convergence results for the reconstruction and motion tracking algorithm presented in Section 4.5.2 are illustrated using Figures 4.S.1 to 4.S.3.

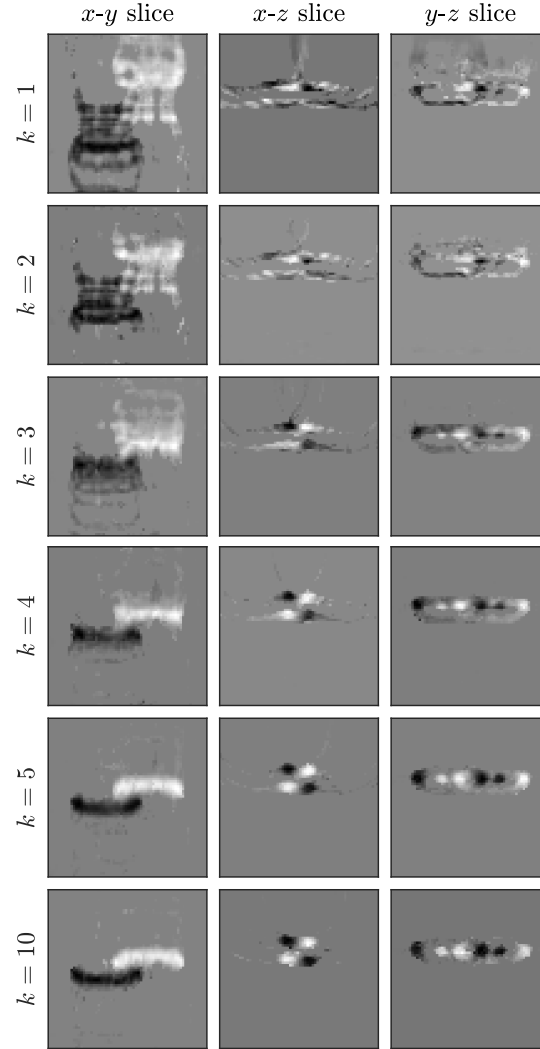


Figure 4.S.1: Cross-sections of reconstructed 3D volume using Algorithm 3. Grayscale images are shown for outer iteration $k = 1, 2, 3, 4, 5$ and 10. The images correspond to $\mathbf{x}_2^{(k)} - \mathbf{x}_1^{(k)}$, the difference between chromophore 1 and chromophore 2 reconstructions. Dimensions are $30\text{mm} \times 30\text{mm}$. The probe coordinate error after outer iteration k is shown in Figure 4.S.2 and Figure 4.S.3.

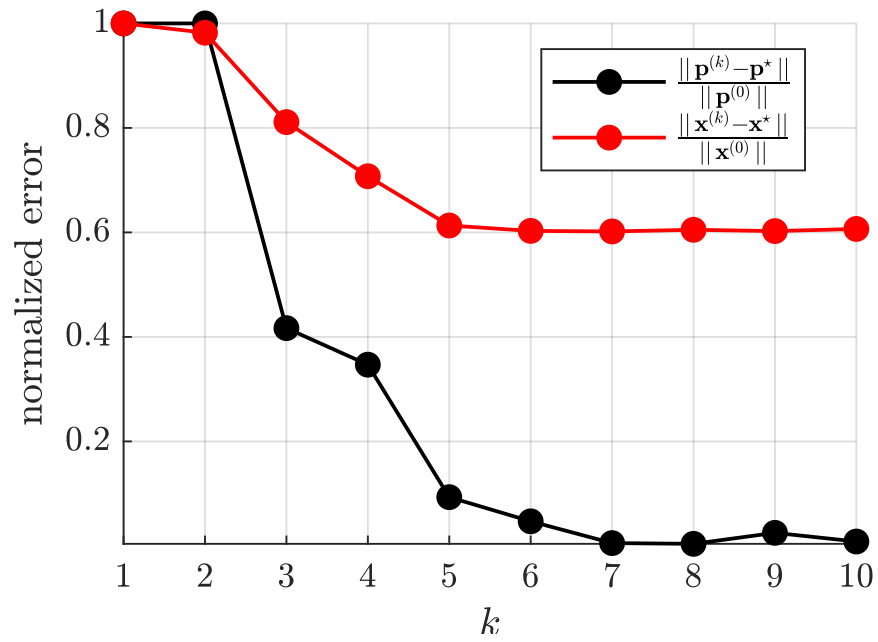


Figure 4.S.2: Normalized error of $\mathbf{p}^{(k)}$ and $\mathbf{x}^{(k)}$ after outer iteration k .

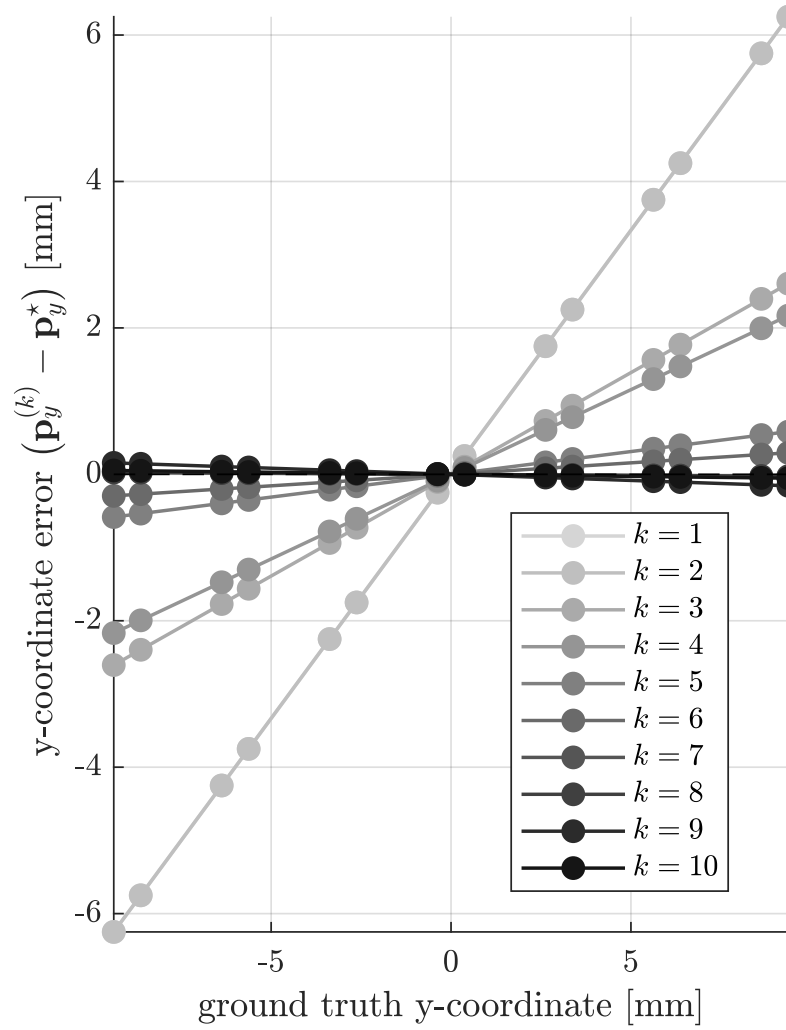


Figure 4.S.3: Position error of y-coordinate after outer iteration k .

4.S.2 Reconstruction using biologically-equivalent phantom

In this section, datasets obtained from a biologically-equivalent phantom are used to compare images reconstructed with mathematical optimization to those reconstructed using 2D backprojection.

In earlier work [4], we constructed the phantom shown in shown in Figure 4.S.4 to characterize performance of an OA system. This involved analyzing 2D images that were reconstructed individually at 757nm and 1064nm wavelengths using a backprojection based approach [4]. The contrast-to-background ratio (CBR) was measured as a function of vessel depth. In addition, a statistical mapping technique [4], [67] was used to display regions of high and low relative blood oxygen saturation (sO_2) using green and red colorization.

Methods

As detailed previously (see Zalev et al. [4]), the phantom consisted of a PVCP (polyvinyl chloride plastisol) background material and two 1.6mm vessels that were filled with bovine blood. A gas mixer and flow system apparatus was used to establish oxygen saturation levels for the vessels of 5% and 99%. Acquisition was performed at 757nm and 1064nm optical wavelengths, using the hand-held OA probe of an investigational Imagio[®] breast imaging system. The probe was mounted on a mechanical actuator to control its position. In the phantom, the vessels were sloped at at 17° incline, which permitted varying the vessel depth in 2D cross-sectional slices (Figure 4.S.4). Vessel depths was varied from 20mm to 44mm. Similar to our previous approach [4], CBR was analyzed as a function of vessel depth. The peak intensity was measured for each vessel as depth

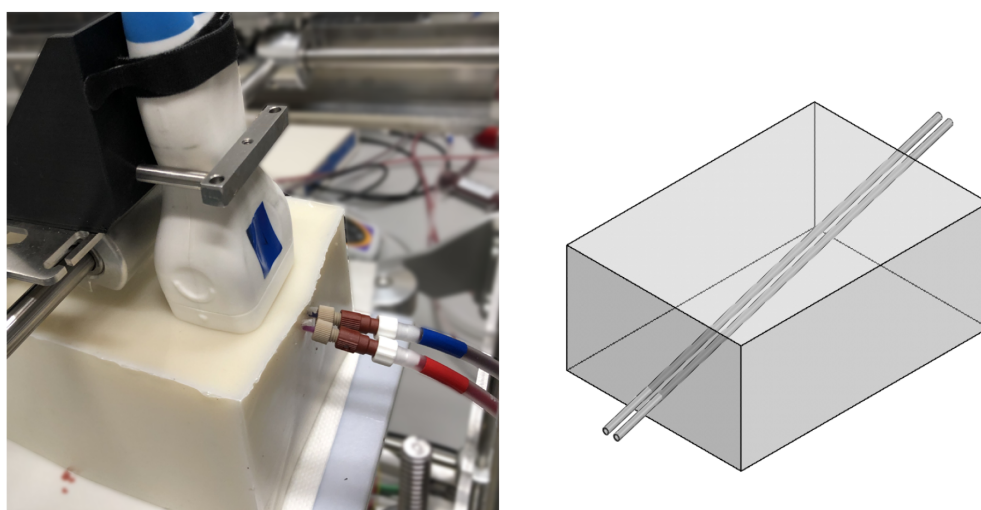


Figure 4.S.4: A biologically-equivalent PVCP phantom consisting of two vessels filled with bovine blood at controlled oxygen saturation levels [4]. Datasets were collected using an investigational Imagio[®] breast imaging system [2], [3]. (left) A hand-held OA probe with linear transducer array is mounted to a mechanical actuator and coupled to the phantom's surface. (right) The vessels are sloped at a 17° incline to permit analyzing CBR vs. depth.

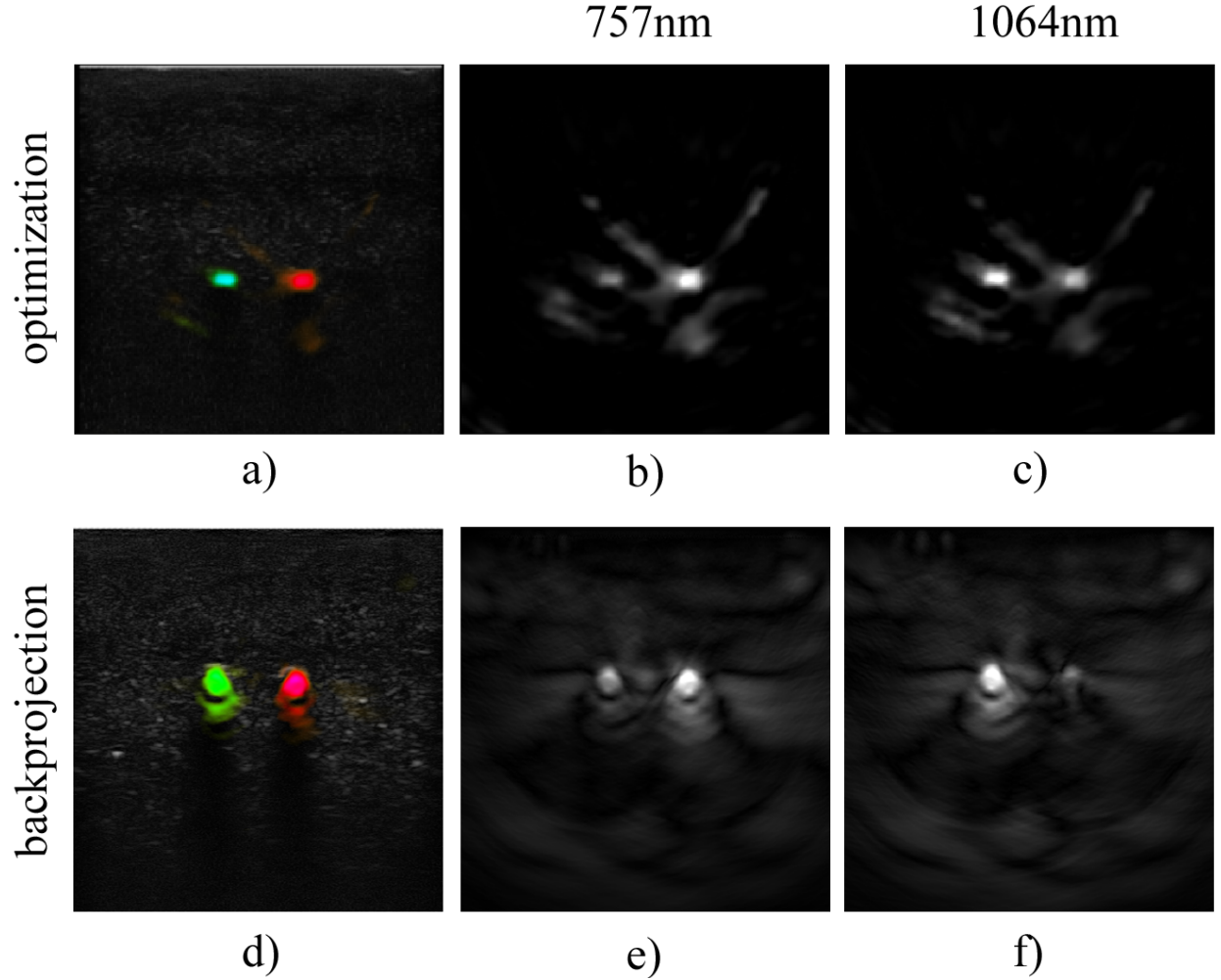


Figure 4.S.5: A reconstructed slice of PVCP phantom, where the two vessels are imaged at 20mm depth. Image dimension is 38×38 mm. Images (a)-(c) are generated using the proposed 3D reconstruction technique. Images (d)-(f) are reconstructed using an approach based on 2D backprojection. In (a) and (d), colored OA data is overlaid on grayscale ultrasound to indicate regions of oxygenated (green) and deoxygenated (red) hemoglobin. In (b) and (e), images correspond to the 757nm optical wavelength. In (c) and (f), images correspond to the 1064nm optical wavelength. Images (d)-(f) were analyzed in earlier work [4].

was varied. To compute CBR, the peak vessel intensity was divided by the average background intensity of an adjacent rectangular window. The CBR was plotted as a function of depth for Vessel 1 (oxygenated) and Vessel 2 (deoxygenated) at 757nm and 1064nm wavelengths. Regions of high and low relative blood oxygen saturation were displayed using statistical mapping. For additional information about color mapping and experimental details, see Zalev et al. (2019) [4].

To evaluate the proposed minimization-based 3D reconstruction technique, the acoustic signal measurements were processed using Algorithm 1. The overall system matrix H was decomposed into F and G as described in equation (4.24). An outer iteration count of $n_{\max} = 1$ was specified. Minimization was solved using TFOCS [66] with 400 inner iterations for F and G . Total variation

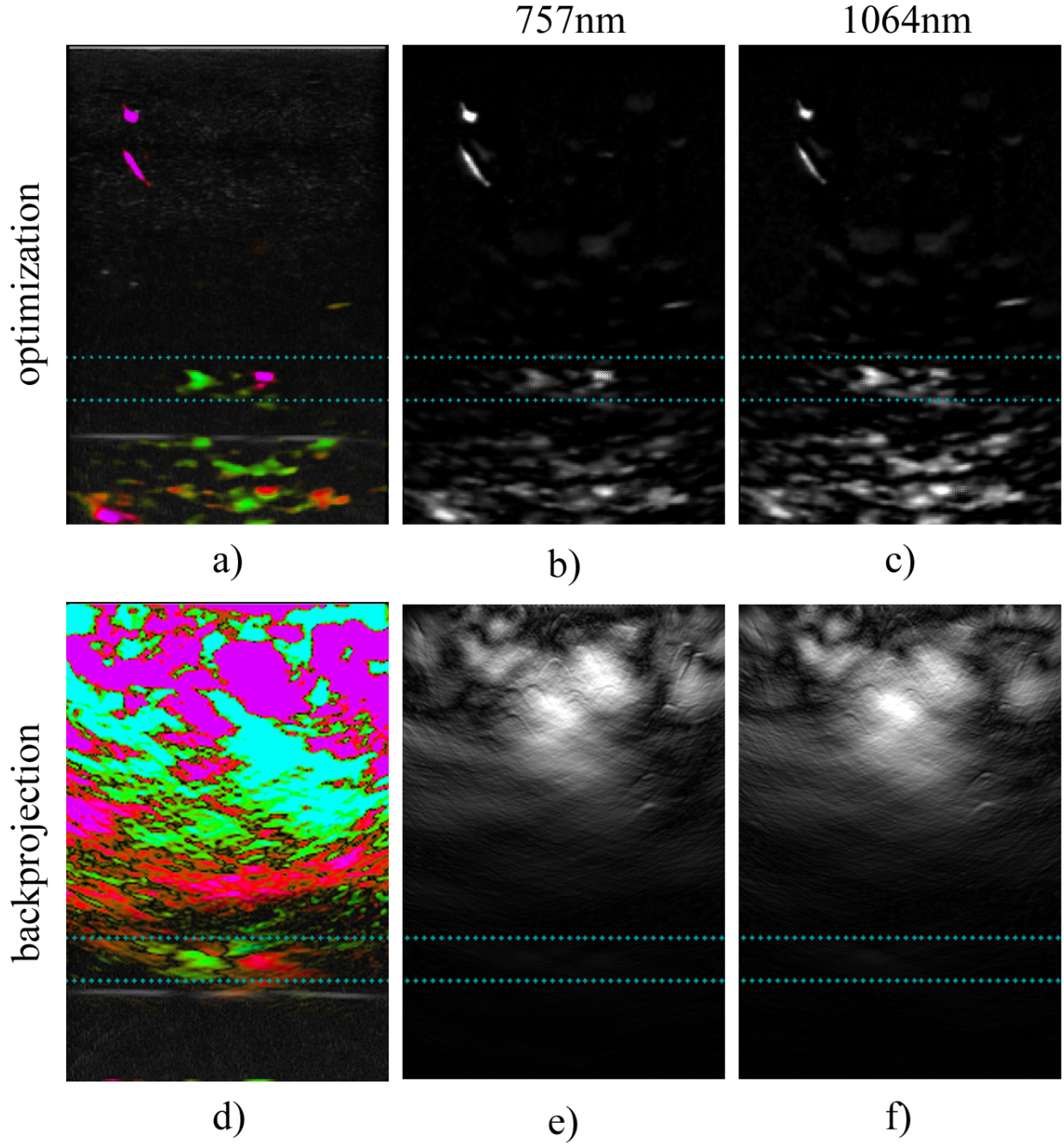


Figure 4.S.6: A reconstructed slice of PVCP phantom, with two vessels imaged at 40mm depth. The vessel location is indicated by dotted lines (cyan). Image dimensions are $38.4 \times 57.6\text{mm}$. The figure layout for (a)-(f) is the same as Figure 4.S.5.

and sparse L1 regularization were used for $\vartheta(\mathbf{x})$. To obtain a sufficiently fine grid size, the 3D reconstruction was split into two separate portions due to the physical length of the phantom and memory limitations. The first portion used a reconstructed volume of size $(256 \times 256 \times 256) \times 2$, with grid spacing 0.15mm/voxel, representing a 38mm cube for each chromophore, which

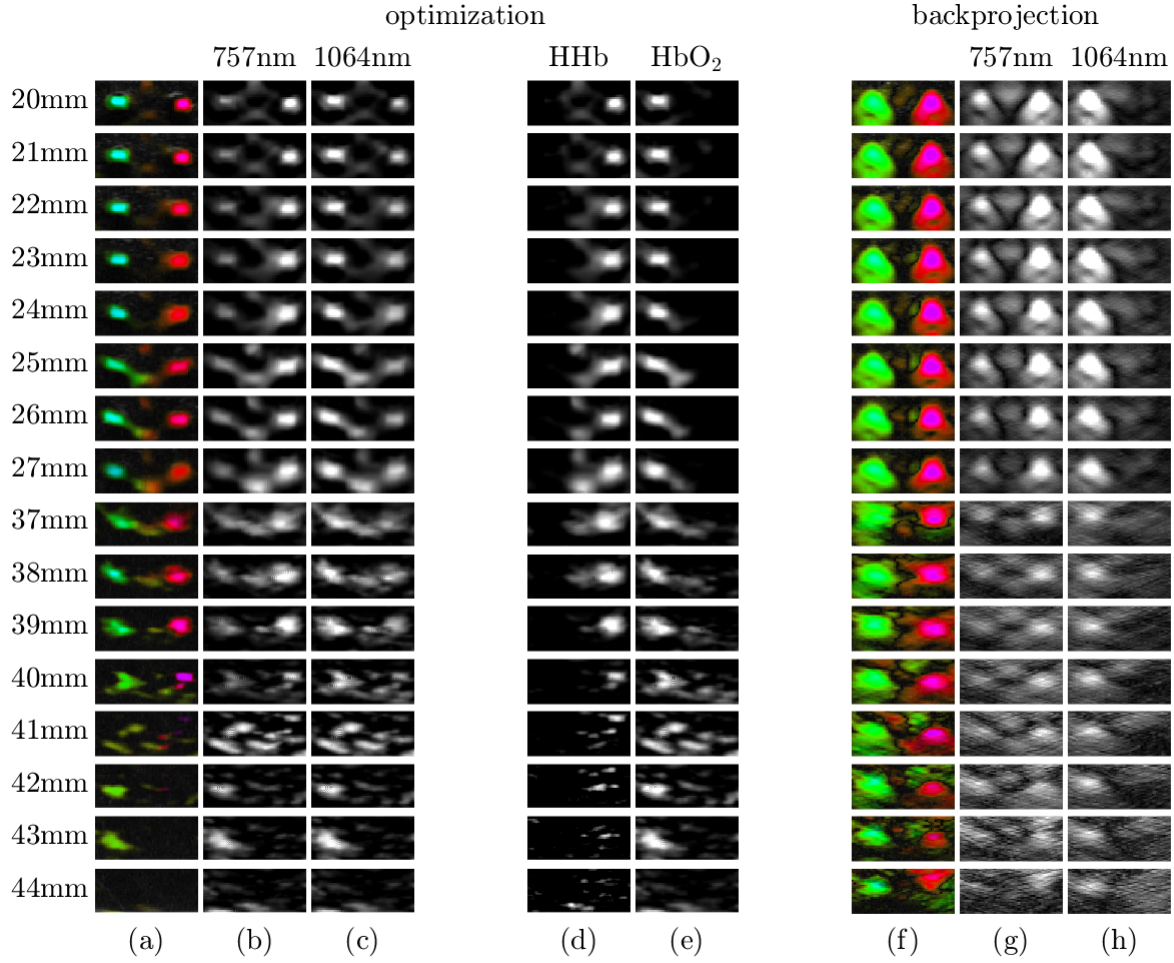


Figure 4.S.7: Reconstruction of two vessels in PVCP phantom as depth is varied. Columns (a)-(e) are generated using the proposed 3D reconstruction technique. Columns (f)-(h) are generated using an approach based on 2D backprojection, which was analyzed in earlier work [4]. The 20mm and 40mm depths correspond to Figures 4.S.5 and 4.S.6. In columns (a) and (f), the OA color map indicates oxygenated (green) and de-oxygenated (red) vessels. Columns (b) and (g) correspond to 757nm optical wavelength. Columns (c) and (h) correspond to 1064nm optical wavelength. CBR ratios obtained from the 757nm and 1064nm images are plotted in Figure 4.S.8. Columns (d) and (e) represent reconstructed HHb and HbO₂ chromophores. Grayscale images are normalized to peak intensity.

captured vessel depths from 20mm to 37mm. The second portion used a reconstructed volume of $(256 \times 256 \times 384) \times 2$, which used an extended depth of 57mm and captured vessel depths from 37mm to 44mm. For each volume, 32 OA frames were acquired with 1.9mm spacing between frames of the same wavelength. The reconstructed chromophore volumes of oxy- and deoxy-hemoglobin were converted to individual 757nm and 1064nm volumes by applying the absorption matrix M_{λ_j} . By examining 2D cross-sections at each wavelength, the CBR was computed at each depth, as described above.

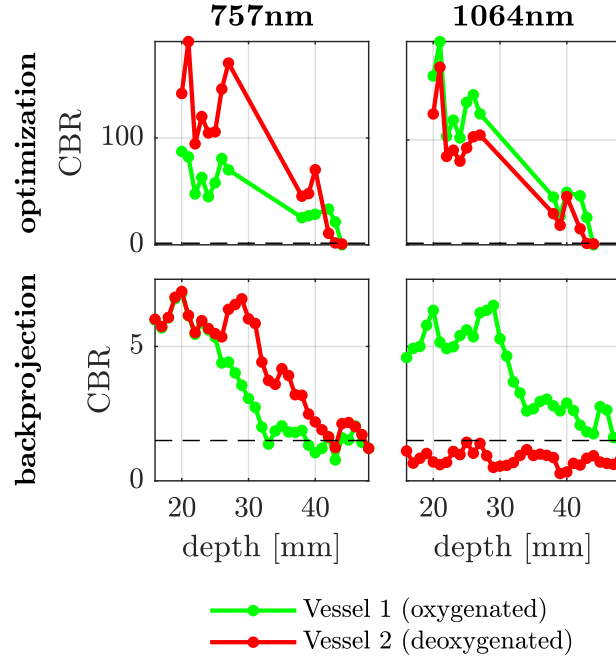


Figure 4.S.8: The contrast-to-background ratio (CBR) of vessels in the PVCP phantom is plotted for the proposed optimization-based technique (top row) and the backprojection-based technique (bottom row). The 757nm optical wavelength (left column) and 1064nm wavelength (right column) plots were obtained using images of Figure 4.S.7. The dotted line indicates the threshold to determine maximum penetration depth.

Results

Reconstruction was computed using mathematical optimization and with backprojection. The OA images are shown using statistically mapped colorization [4], [67], and for individual 757nm and 1064nm wavelengths. Figure 4.S.5 displays the reconstructed cross-sections for 20mm vessel depth. In Figure 4.S.6, the cross-sections are displayed at 40mm vessel depth. Figure 4.S.7 graphically illustrates the vessels at each depth for both types of reconstruction. In Figure 4.S.7, the grayscale images are normalized to peak intensity of each window to highlight viability of vessels and background. Figure 4.S.8 plots the corresponding CBR vs. depth. A CBR threshold of 1.5 was used to determine the maximum penetration depth. A 3D reconstruction of the phantom is shown in Figure 4.S.9, which is plotted using the isocontours of the difference between HHb and HbO₂ chromophores.

Discussion

In Figures 4.S.5 and 4.S.6, a background with reduced overall clutter is observed when mathematical optimization is used, compared to the backprojection based approach. However, with mathematical optimization, there was minor additional streak artifact, likely due to acoustic

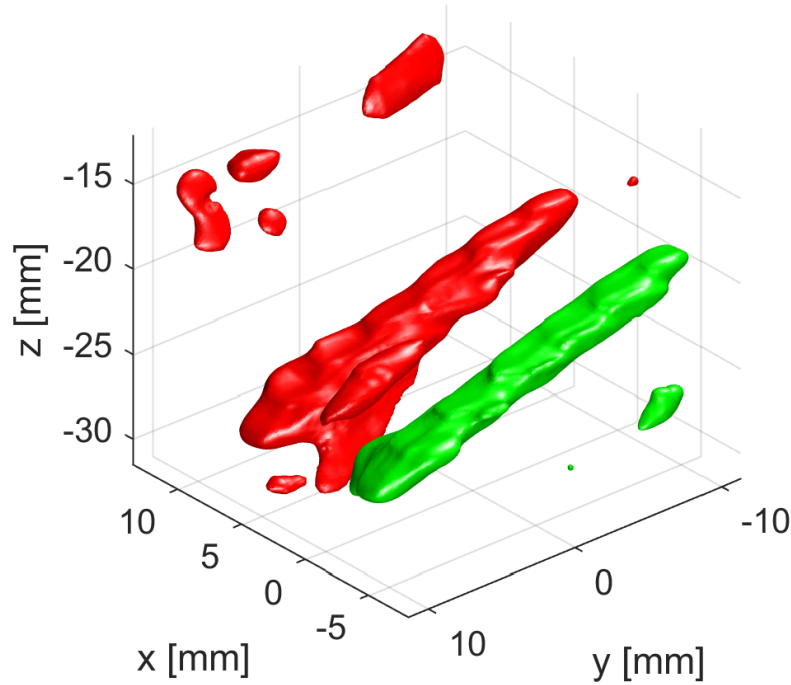


Figure 4.S.9: 3D reconstruction of PVCP phantom. Isocontour surfaces of the 3D chromophore difference map $\mathbf{x}_{\text{HHb}} - \mathbf{x}_{\text{HbO}_2}$ are displayed to indicate oxygenated (green) and deoxygenated (red) hemoglobin.

reverberations within the phantom, which is seen in Figure 4.S.5 at 20mm depth adjacent to the vessels. It is possible that with backprojection, this type of artifact was present, but masked by low CBR, falling below the background noise floor. In Figure 4.S.6, backprojection produced artifact due to strong near-field fluctuations. This was amplified by normalization to peak image intensity, which reduced visibility of the 40mm depth vessels because they have lower intensity than the near-field artifact. However, the CBR and near-field artifact was substantially improved using mathematical optimization. In Figure 4.S.7, each displayed window region is normalized to its own peak intensity. This enhances visualization of the vessel and background, but does not alter the CBR calculation. The CBR is plotted by depth in Figure 4.S.8. In the near- and mid-field, the CBR improves for 3D mathematical optimization compared to 2D backprojection by a factor of ~ 20 . However, in Figure 4.S.8, mathematical optimization had an abrupt transition in visualization at 44mm depth, when the CBR fell below a certain level, at which point it could no longer detect the vessels. When backprojection was used, although the CBR was much lower overall, the transition of vessel intensity into the background was more gradual with increasing depth. This suggests that the proposed approach can significantly improve CBR, provided that a target has sufficient signal strength to be distinguished from the background. In future work, further performance testing and phantom-based system characterization will be performed.

4.S.3 Reconstruction of digital phantom with multi-frame acquisition and monochromatic illumination

In this section, we investigate using the model of Section 4.3 to suppress out-of-plane artifact and perform accurate reconstruction.

Methods

To simplify analysis, we used a model with monochromatic illumination, i.e., the same optical wavelength for all frames. This makes it possible to isolate effects that occur by varying the number of frames and transducer geometry; however, it prevents differentiating chromophores, so only one material is used. In this simplified case, M_{λ_j} in equation (4.14) is reduced to the identity matrix, and $n_\mu = n_\lambda = 1$. Consequently, the reconstructed volume $\mathbf{x}$ represents the variables η , μ_a and χ_i in equations (4.2) and (4.3) to within a constant scaling factor of each other, which makes the results applicable to all three variables.

Simulation was performed on a 3D digital phantom consisting of two spherical absorbers, as shown in Figure 4.S.10. This phantom is designed to produce out-of-plane artifact, since one sphere generates acoustic interference when the probe is positioned over the other. The spheres have 10mm diameter, a 16mm center depth, and a homogeneous optical absorption coefficient μ_a of 1 arbitrary unit. The background was assumed to have negligible absorption. The simulated volume had $256 \times 256 \times 128$ voxels, with grid spacing 0.5mm/voxel. Motion was simulated for the linear array using a constant velocity trajectory, which acquired 15 frames of data over a swept aperture of 20mm, as shown in Figure 4.S.10c. 2D cross-sections of the phantom's x-z and y-z planes are shown in Figure 4.S.11.

From the simulated measurements, datasets consisting of 1, 3 and 15 frames were used for analysis. In addition, two transducer geometries were evaluated separately: i) “wide”, a 0mm width ideal point aperture, and ii) “ideal”, a thin transducer with an elevational width of 4mm.

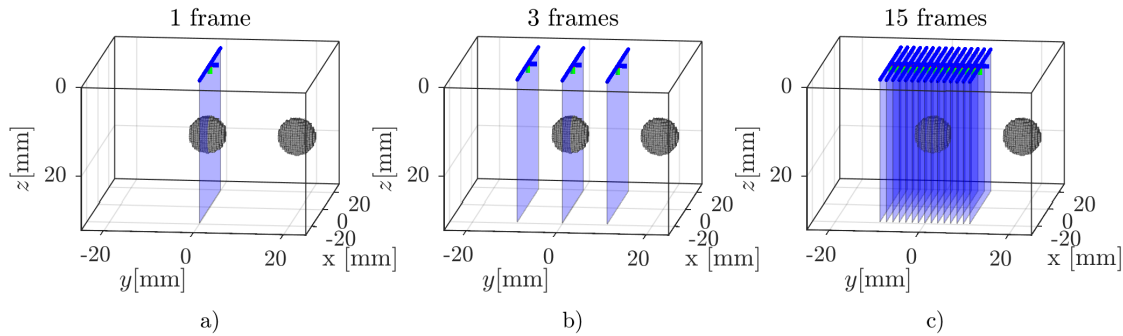


Figure 4.S.10: 3D volume with spherical absorbers. A linear array (blue line) acquires (a) 1 frame, (b) 3 frames, and (c) 15 frames. The imaging plane (light blue) is shown for each frame.

Both transducer geometries used cosine directivity α as specified in equation (4.8) and an ideal electro-mechanical impulse response $\beta(t) = \delta(t)$. The radiant fluence φ was assumed to be homogeneous (constant).

Reconstruction used a 3D volume with $128 \times 128 \times 128$ voxels and grid spacing 1mm/voxel, which is different from the grid used in simulation. We analyzed the ability to localize both spheres and suppress interference from the out-of-plane sphere. Two methods for reconstruction were compared: i) performing minimization using Equation (4.27); and, ii) performing back-projection based on the operator adjoint of Equation (4.15). For both reconstruction methods, the model's transducer geometry was varied between ideal and wide element sizes. By using different geometries for reconstruction and simulation, this permits analyzing mismatch between the measurements y and the reconstruction's model H .

Results

The time-domain signals from probe location $y = 0$ are shown in Figure 4.S.12, simulated for each transducer geometry. The spheres produced "N-shaped" waveforms, which was expected. The wide transducer provides increased directionality, which filters out more signal from the out-of-plane sphere.

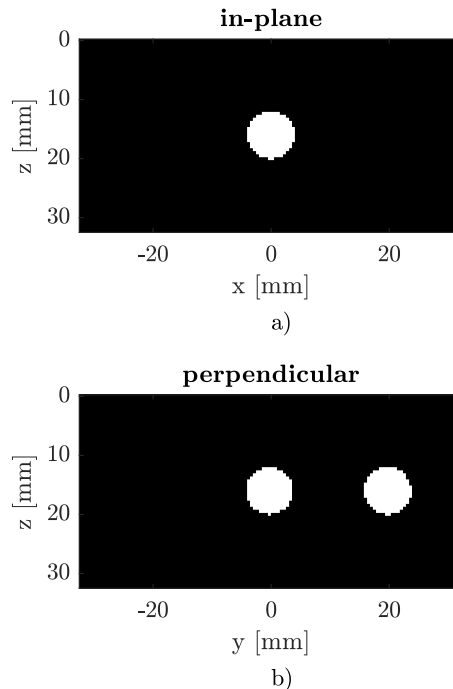


Figure 4.S.11: Cross-sections of 3D volume with two spherical absorbers. (a) The $y = 0$ slice (indicated as imaging plane in Figure 4.S.10a). (b) The perpendicular $x = 0$ slice (not illustrated in Figure 4.S.10). The black background indicates no optical absorption. The white targets have homogeneous optical absorption in arbitrary units.

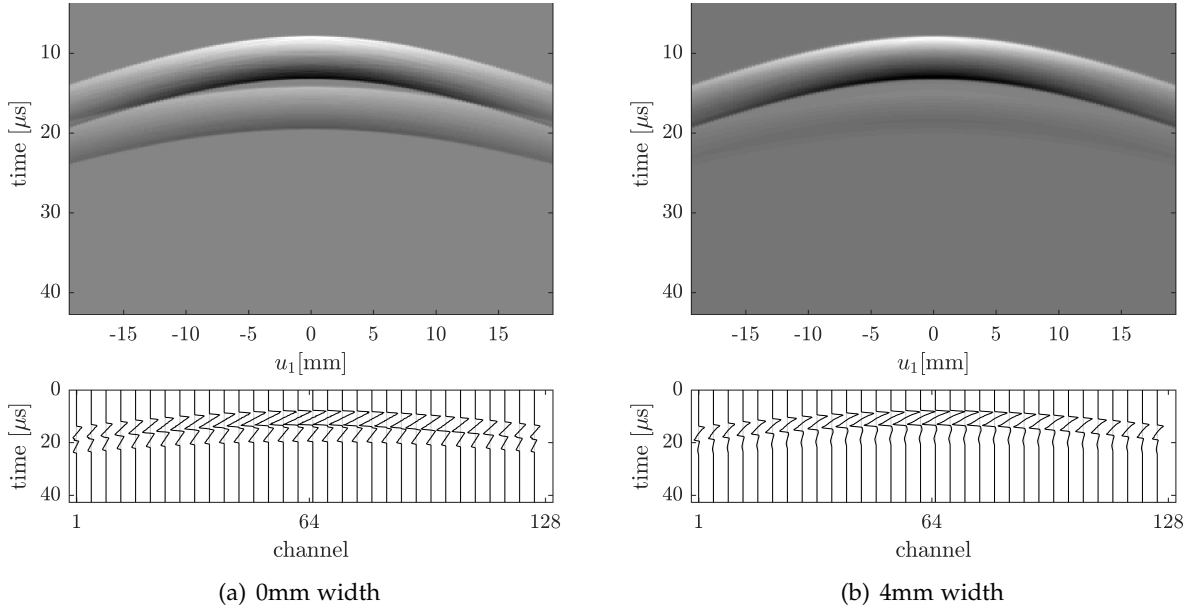


Figure 4.S.12: Simulated data for linear array. Time domain data is shown graphically (top) and plotted (bottom). The array is positioned as shown in Figure 4.S.10a. The transducer elements are modeled using (a) an ideal point-aperture and (b) a 4mm wide aperture. The time-domain plots (bottom) illustrate that each spherical absorber generates an N-shaped waveform, which arrives earlier for the in-plane absorber than the out-of-plane absorber. The out-of-plane waveform is weaker in (b) compared to (a) because the transducer aperture acts as a spatially-dependent filter.

To analyze results from reconstruction, PSNR (peak signal-to-noise ratio) is computed compared to the ground truth of Figures 4.S.10 and 4.S.11. In each case, the number of frames (1, 3 or 15) and reconstruction method (mathematical optimization vs. back-projection) were varied. Reconstructed cross-sections of the three cases considered are shown in Figures 4.S.13, 4.S.14 and 4.S.15. Horizontal and vertical profiles of image intensity are summarized in Figures 4.S.16 and 4.S.17. Table 4.S.1 summarizes results obtained by measuring PSNR in each 3D reconstructed volume.

Discussion

The results used monochromatic illumination to demonstrate performance using multi-frame acquisition. The number of frames, reconstruction method and transducer geometry were varied to isolate their effects. We considered three cases, where simulation and reconstruction used different models (summarized in Table 4.S.1). In Case 1 (Figure 4.S.13), the simulated dataset representing ideal measurement was used as input to the ideal reconstruction model. In Case 2 (Figure 4.S.14), the ideal input from Case 1 was applied to the wide element reconstruction model. This represents a situation corresponding to “real-world” data being used in an idealized reconstruction, which involves substantial mismatch between measurement and model. Consequently, there is lower PSNR for this case compared to the others. In Case 3 (Figure 4.S.15), the wide transducer dataset

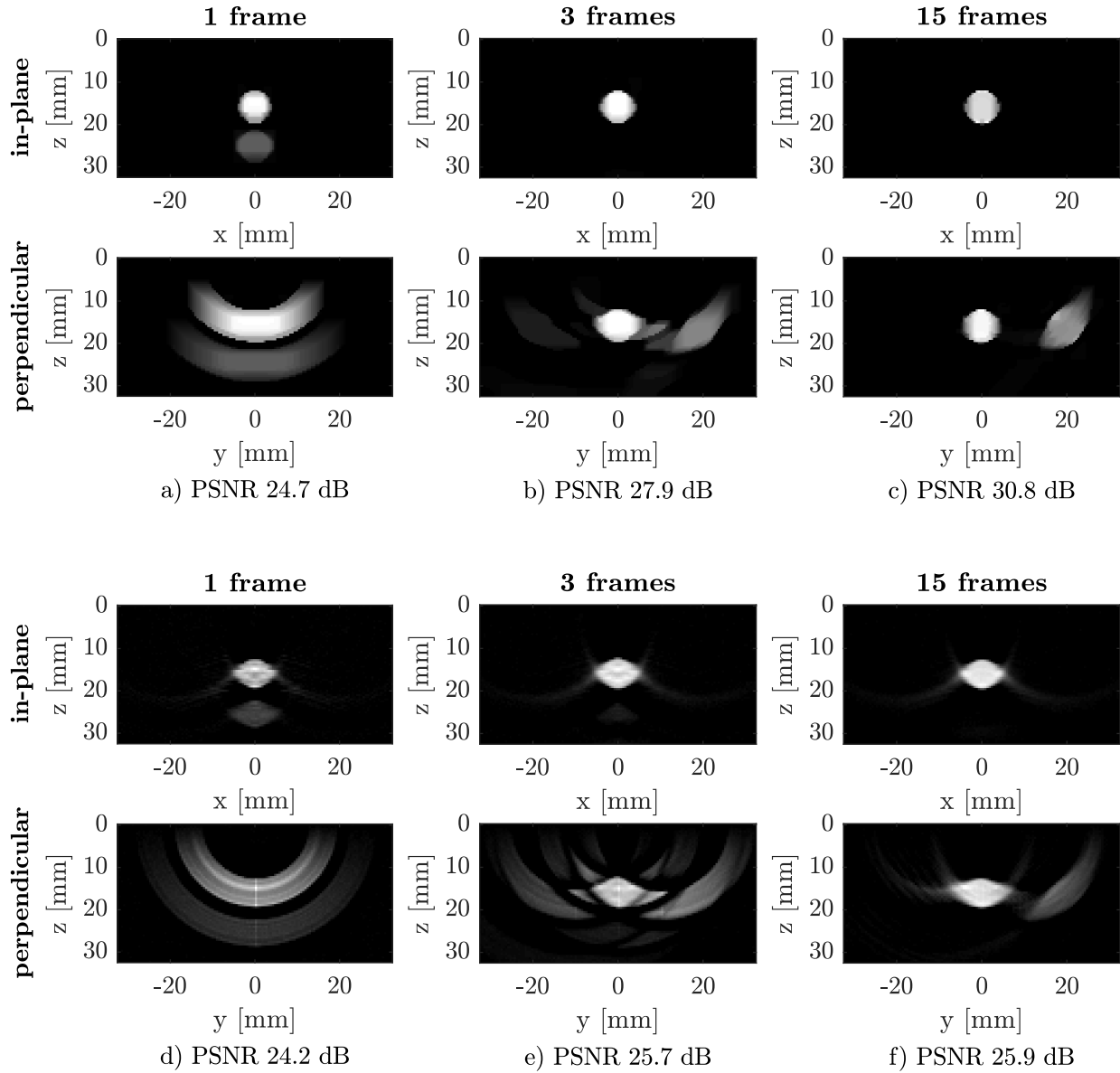


Figure 4.S.13: 3D reconstruction of spherical absorbers (Case 1: ideal measurement/ideal model). The simulated measurement and model for reconstruction both used an ideal transducer aperture. The linear array was positioned as shown in Figure 4.S.10. In each subplot, the reconstructed volume's in-plane cross-section ($y = 0$) and perpendicular cross-section ($x = 0$) are shown. The number of frames and reconstruction method was varied. In (a)-(c), reconstruction is performed using mathematical optimization. In (d)-(f), reconstruction is performed using a back-projection based approach. Horizontal and vertical profiles are plotted in Figures 4.S.16 and 4.S.17.

is applied to a wide transducer model. In Figures 4.S.13 to 4.S.15, the in-plane ($y = 0$) and perpendicular ($x = 0$) cross-sections of volume x are shown when reconstructed using the prosed optimization-based method and when using backprojectection. The in-plane sphere, centered at $x = y = 0$, represents “true signal” occurring in both cross-sections. The out-of-plane sphere, which

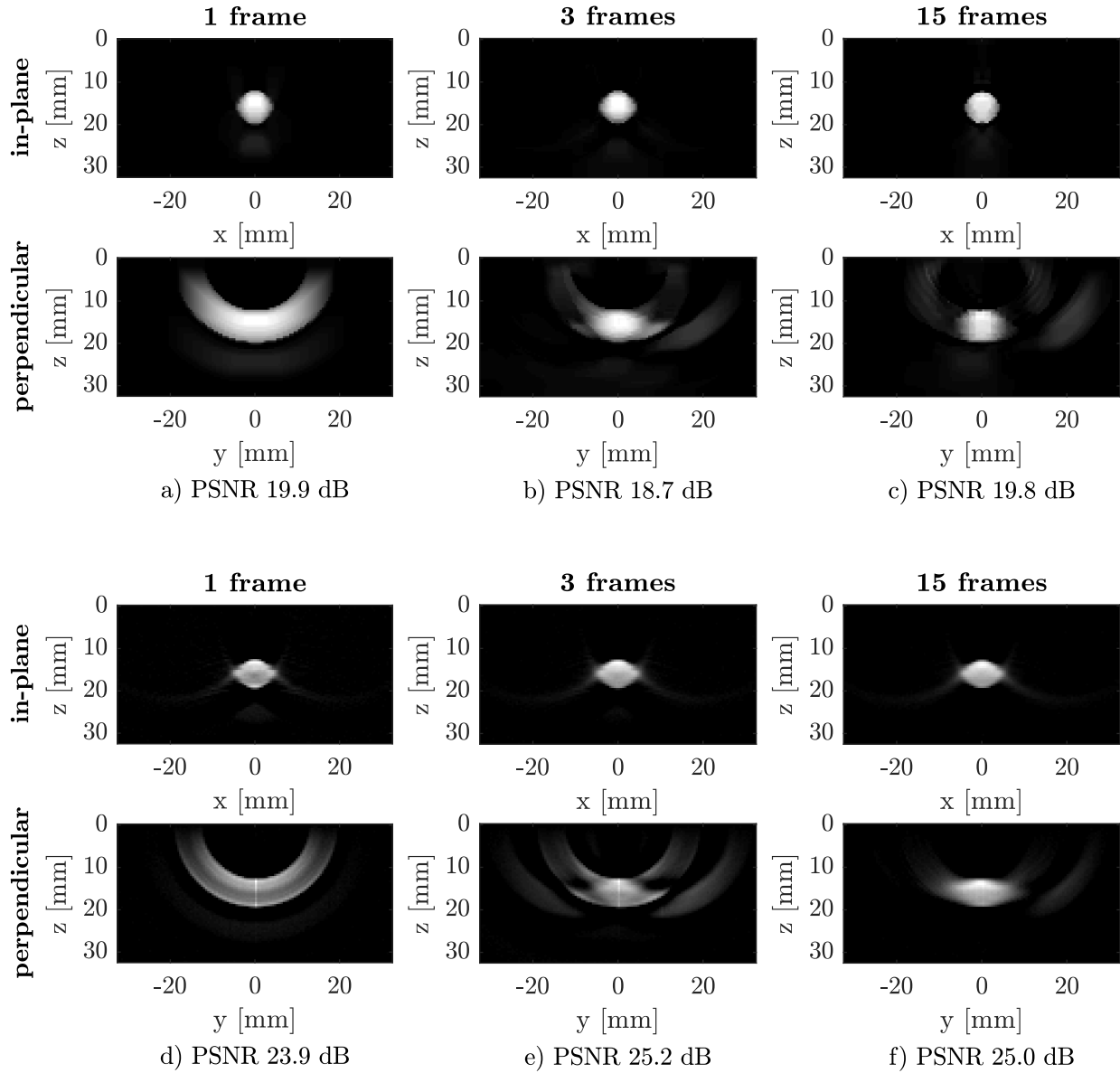


Figure 4.S.14: 3D reconstruction of spherical absorbers (Case 2: wide measurement/ideal model). The simulated measurement used a 4mm wide aperture and the model for reconstruction used an ideal transducer aperture. Subplots (a)-(f) have same arrangement as Figure 4.S.13.

generates true signal in the out-of-plane cross-section, produces interference in the in-plane cross-section centered at depth 24mm. The vertical profile in Figure 4.S.17 permits analyzing the relative intensities of true signal to out-of-plane interference. Figures 4.S.13 to 4.S.16 illustrate that when more frames are acquired, the ability to localize either sphere in the perpendicular cross-section is improved. In the reconstructions, using mathematical optimization reduces geometric distortion resulting in more accurate reconstruction of circular features compared to back-projection. The ability to localize acoustic sources to the imaging plane is also improved with mathematical

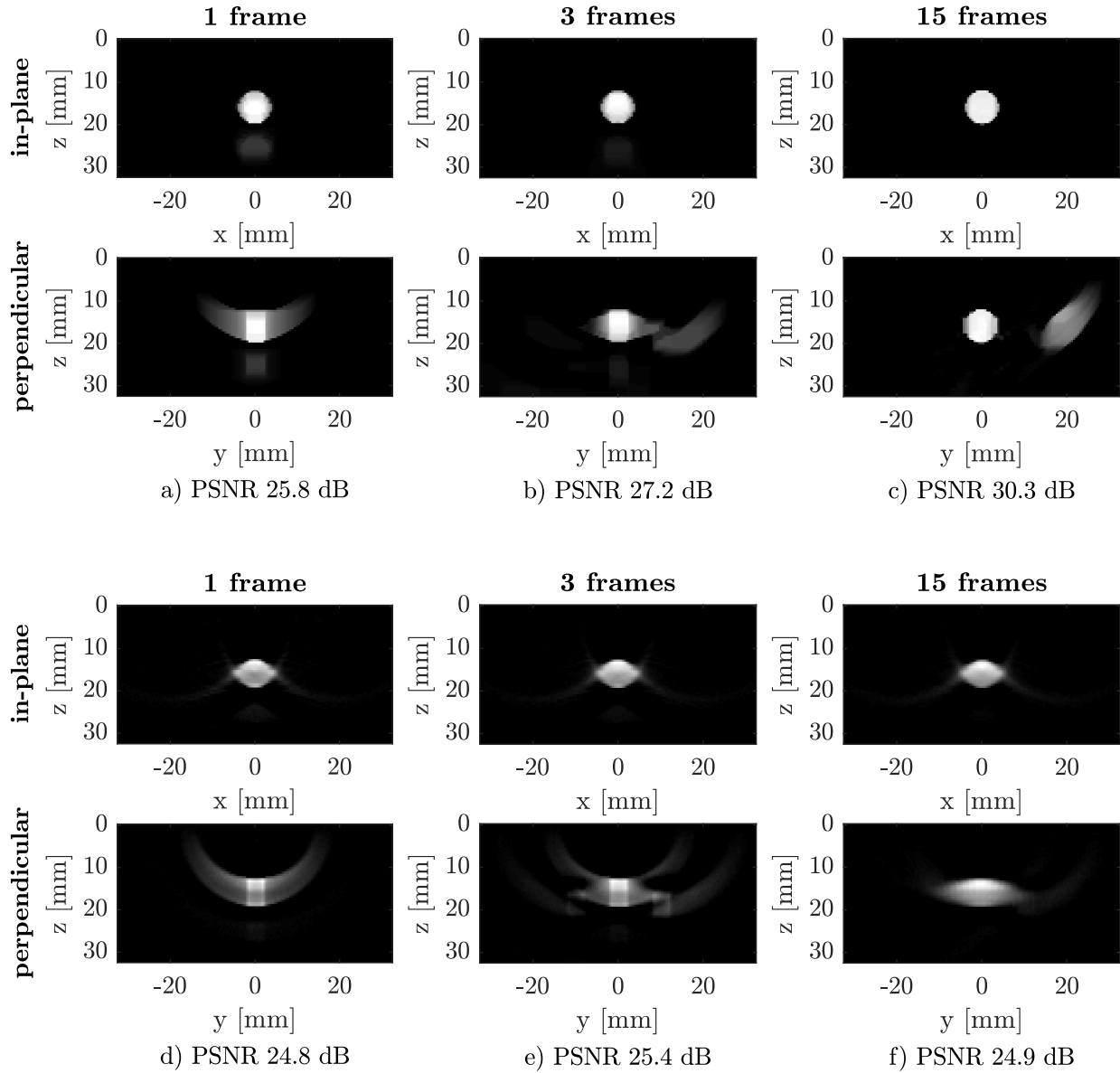


Figure 4.S.15: 3D reconstruction of spherical absorbers (Case 3: wide measurement/wide model). The simulated measurement and model for reconstruction both used a 4mm wide aperture. Subplots (a)-(f) have same arrangement as Figure 4.S.13.

optimization. When the spacing between frames is too high, this can result in side-lobe artifact. This occurs in the perpendicular cross-section with greater intensity for 3 frame acquisition compared to 15 frame acquisition, and it is improved with mathematical optimization compared to back-projection. The 1 frame acquisition produces a single arc-shaped lobe that is not well localized in the perpendicular cross-section. The wide transducers resulted in reduced out-of-plane interference, which is observed in Figures 4.S.14 and 4.S.15 compared to Figure 4.S.13.

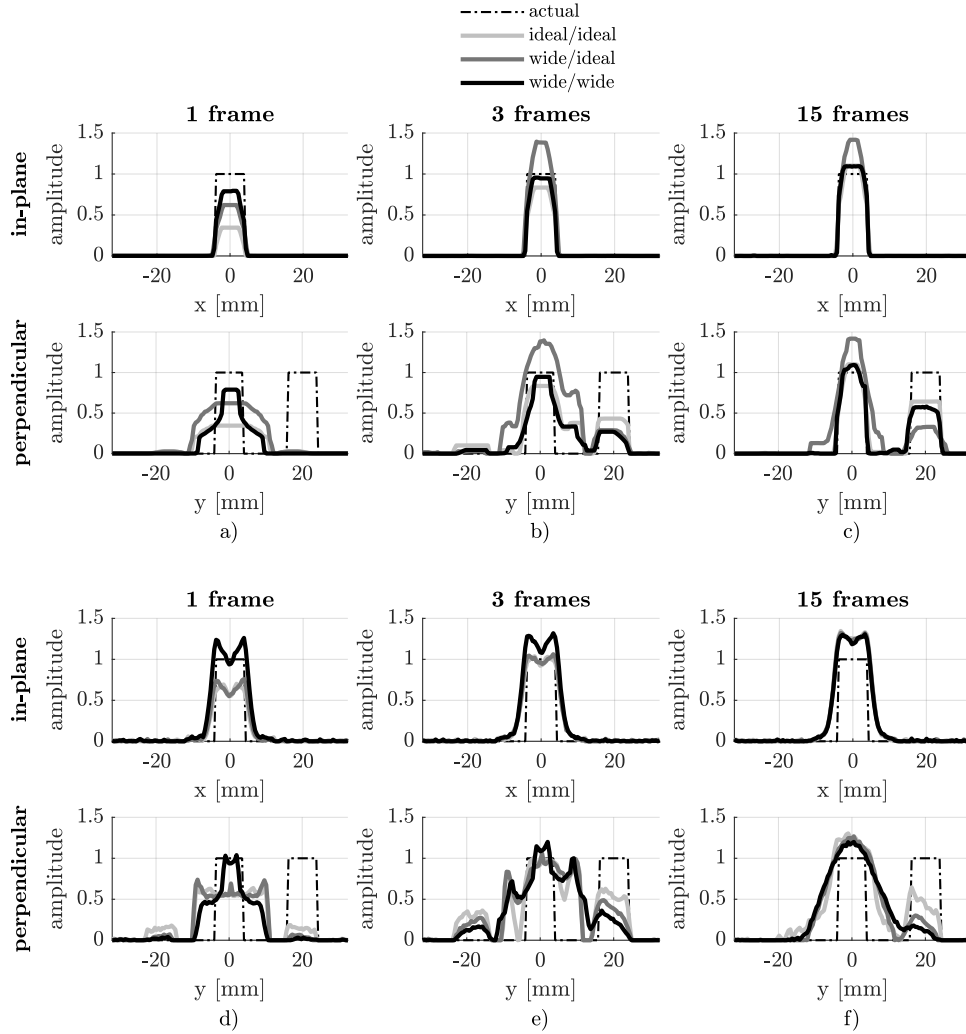


Figure 4.S.16: Horizontal profile of reconstructed spherical absorbers at $z = 16\text{mm}$ depth. Data corresponds to Figures 4.S.13 (ideal/ideal), Figure 4.S.14 (wide/ideal) and Figure 4.S.15 (wide/wide). Dotted line represents actual profile. The number of frames and reconstruction method is varied. In (a)-(c), reconstruction is performed using mathematical optimization. In (d)-(f), reconstruction is performed using a back-projection based approach.

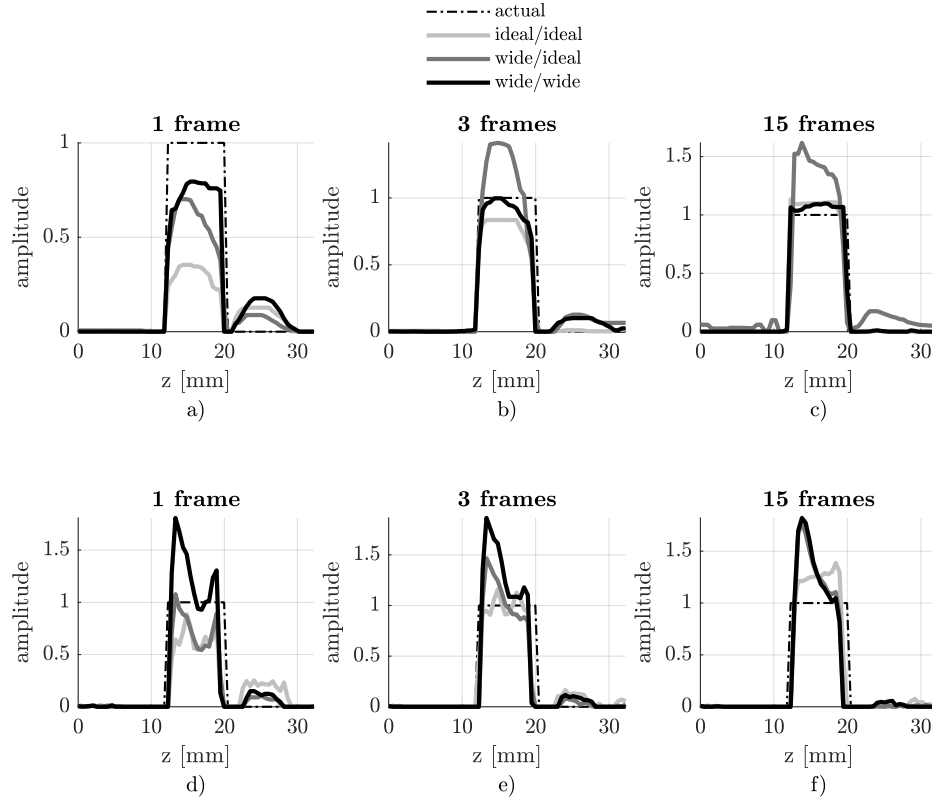


Figure 4.S.17: Vertical profile of reconstructed spherical absorbers. Data corresponds to the line $x = y = 0\text{mm}$ in Figure 4.S.13 (ideal/ideal), Figure 4.S.14 (wide/ideal) and Figure 4.S.15 (wide/wide). The vertical profile is identical for in-plane and perpendicular cross-sections, so this is plotted once. Dotted line represents actual profile. Signal from out-of-plane interference is centered at depth $z = 24$. The number of frames and reconstruction method is varied. In (a)-(c), reconstruction is performed using mathematical optimization. In (d)-(f), reconstruction is performed using a back-projection based approach.

Table 4.S.1: Summary of PSNR for 3D reconstructed volumes.

Case	Figure	Frames	PSNR Optimization	PSNR Backprojection
1. ideal/ideal	4.S.13	1	24.7 dB	24.2 dB
		3	27.9 dB	25.7 dB
		15	30.8 dB	25.9 dB
2. wide/ideal	4.S.14	1	19.9 dB	23.9 dB
		3	18.7 dB	25.2 dB
		15	19.8 dB	25.0 dB
3. wide/wide	4.S.15	1	25.8 dB	24.8 dB
		3	27.2 dB	25.4 dB
		15	30.3 dB	24.9 dB

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ABSTRACT

In certain imaging systems, acquired raw data is pre-processed with a filtering stage before being processed with an image reconstruction stage. During these sequential stages, distortions may arise if valid signal cannot adequately be distinguished from interference. To avoid these distortions, a mixed-domain proximal operator is mathematically formulated, which permits interference to be separated from data concurrently during a combined processing stage. The technique is demonstrated with an application involving opto-acoustic imaging. Reconstruction is performed with an accelerated proximal gradient method. Total-variation minimization is used to promote smoothness in the image domain. In the data domain, interference is modelled as a low-rank matrix, which corresponds to a few time dependent interference components being coupled to each channel by determined amounts. Results are presented that demonstrate the ability to separate interference on a digital phantom used to simulate opto-acoustic signals.

5.1 INTRODUCTION

In imaging systems, acquired raw data typically contains a desired target signal as well as undesired electro-magnetic interference (EMI). To obtain the highest image quality, the EMI is filtered or removed from the desired target signal. In sequential processing approaches, EMI is filtered out prior to image reconstruction. However, this may be sub-optimal because the presence of target signal in the data can create errors in estimation and removal of EMI, leading to artifacts.

In the proposed approach, interference removal and image reconstruction are performed concurrently. This is done by minimizing a combined objective function that describes signal generation and EMI models separately. The combined objective function is designed to identify data components that fit either the signal generation model or the EMI model. This helps to avoid image artifact that might otherwise be caused.

In this letter, a new derivation using proximal operators is described that allows concurrent minimization of combined objective functions. It is shown how to formulate the optimization problem when its form is mixed between the *image domain* and *data domain*. This allows application of existing proximal gradient algorithms [1]–[7] to obtain a solution.

Opto-acoustic imaging is a new modality that has recently been investigated clinically for improved accuracy in breast cancer diagnosis [8]–[10]. In opto-acoustic imaging, an ultrasonic transducer array records time-domain acoustic signals caused by thermal expansion in response to a laser pulse [11]. Acoustic waves propagate from each position in the imaged object to a sensor associated with each channel, as described in Section 5.5. In electronic hardware, when multiple channels of data are sampled simultaneously, EMI is correlated between each channel. Accordingly, our EMI model corresponds to a low-rank matrix that represents the coupling of a common time-domain interference to each channel.

Removal of a common time-domain interference is possible by several other approaches. It can be achieved by applying pre-processing operations that filter out EMI prior to further processing of the target signal, or in some cases, with post-processing afterward. Such approaches include: removing stripes by applying a frequency domain filtering [12]; combined wavelet and FFT based stripe filtering [13]; minimization approaches, where stripes are defined to vary slowly along one direction [14]; adaptive filtering [15]; projecting stripe noise on to an orthogonal basis of eigenvectors, i.e. using principal component analysis, singular-value decomposition, or Karhunen-Loeve transform [16]; and, robust principal component analysis (RPCA), where a matrix is decomposed into low-rank plus sparse components [17], [18]. In addition, numerous approaches exist for iterative image reconstruction on filtered or unfiltered data [1]–[6]. Various proximal splitting methods for solving signal processing problems are compared by Combettes et al. (2011) [5], including those where multi-term objective functions are used. Gradient based algorithms for total-variation (TV) regularization that were applied separately in mixed-domains were implemented by Burger et al. (2014) using a multi-term objective function, and the solution involved solving five decoupled minimization problems at each iteration [19]. Approaches for image denoising have also been

studied where the noise is a combination of two different distributions [20]. In opto-acoustic imaging, various analytical [21]–[23] and minimization based [24], [25] approaches have been described for image reconstruction.

To our best knowledge, the proposed approach of concurrent interference separation and image reconstruction using a mixed-domain proximal operator is a new result that has not been described elsewhere. Our derivation is performed at a relatively high level of abstraction and permits fast proximal gradient methods to solve large-scale problems of this form.

$$\begin{aligned}
 x &\in \mathbb{R}^{(N_x N_y N_z)} \equiv \text{reconstructed image vector} \\
 y &\in \mathbb{R}^{(N_s M)} \equiv \text{noise removed data vector} \\
 H &\in \mathbb{R}^{(N_s M) \times (N_x N_y N_z)} \equiv \text{system matrix} \\
 N_s &\equiv \text{number of samples} \\
 M &\equiv \text{number of channels} \\
 N_x N_y N_z &\equiv \text{number of pixels} \\
 B = [b_1, \dots, b_M] &\in \mathbb{R}^{N_s \times M} \equiv \text{data matrix} \\
 P = uv^T &\equiv \text{rank-1 noise approximation}
 \end{aligned}$$

5.2 PROBLEM FORMULATION

In the proposed approach, the combined image reconstruction and EMI removal process is formulated as an optimization problem defined by

$$\begin{aligned}
 &\underset{x, u, v}{\text{minimize}} \quad \|Hx - y\|_2^2 + \alpha_1 \Phi(x) + \alpha_2 \|B - P\|_F^2 \\
 &\text{subject to} \quad y = \text{vec}(B - P), \quad P = uv^T.
 \end{aligned} \tag{5.1}$$

Here, the sampled measurements are represented as a matrix $B = [b_1, \dots, b_M] \in \mathbb{R}^{N_s \times M}$. Each vector $b_i \in \mathbb{R}^{N_s}$, $i = 1, \dots, M$ represents one of the M simultaneously acquired channels of data. There are N_s samples of data per channel. The vector $y \in \mathbb{R}^{(MN_s)}$ represents the interference removed signal after EMI has been subtracted from the channel data matrix, rearranged as a column vector. The reconstructed image vector, which is an unknown variable, is represented by $x \in \mathbb{R}^{(N_x N_y N_z)}$. Here, N_x , N_y and N_z are the number of voxels in the x , y and z directions, so $N_x N_y N_z$ is the total number of voxels in the reconstructed image. The system matrix $H \in \mathbb{R}^{(N_s M) \times (N_x N_y N_z)}$ is the forward imaging operator that predicts what signal will be received for any particular image vector. Thus H describes the signal generation model. In equation (5.1), the term $\|Hx - y\|_2^2$, minimizes the squared Euclidean distance between the predicted signal and the estimate of x . The vec operator is used to rearrange ordered elements in a matrix as a vector, which forms $y = \text{vec}(B - P)$.

The unknown vector $u \in \mathbb{R}^{N_s}$ represents the common EMI, and the unknown vector $v \in \mathbb{R}^M$ represents the amount of EMI that couples to each channel. The Frobenius norm $\|\cdot\|_F$ is used to minimize the distance $\|B - P\|_F$. Therefore, the matrix $P = uv^T$ is constrained to be the closest rank-1 matrix approximation to B . Since the constraint $P = uv^T$ causes the matrix to be rank-1, the problem is non-convex (rank constraints are non-convex). Nevertheless, the approach below can be shown to converge to a solution due to the chosen proximal operators.

In (5.1), the EMI is assumed to be rank-1, which is sufficient to demonstrate the mixed domain approach. However, this can be extended to higher rank generalizations that describe more complex interference patterns. To use a rank- r interference model, the vector $u \in \mathbb{R}^{N_s}$ can be replaced with a tall matrix $U \in \mathbb{R}^{N_s \times r}$, and $v \in \mathbb{R}^M$ can be replaced with a tall matrix $V \in \mathbb{R}^{M \times r}$, so that $P = UV^T$. The proximal formulation below is sufficient to be used with general rank- r matrices.

The function $\Phi(x)$ is a penalty function used for regularization in the image domain. In our implementation, the isotropic total variation penalty function $\Phi_{TV}(x)$ (see [6]) is used to promote spatially smooth solutions. The constants α_1 and α_2 are regularization parameters.

5.3 ACCELERATED PROXIMAL GRADIENT

To solve equation (5.1), a technique based on accelerated proximal gradient (APG) methods [1]–[7] is used. When the system matrix H is large (which makes second-order methods less practical), first-order accelerated gradient methods can be used to provide efficient implementation.

Proximal gradient approaches are useful when an objective function $f_0(x)$ can be split into a smooth differentiable function $f(x)$ plus a non-smooth function $g(x)$. In this case, the optimization problem

$$\underset{x}{\text{minimize}} \quad f_0(x) = f(x) + g(x) \quad (5.2)$$

can be solved by an iterative technique. In each iteration, it is required to compute the gradient $\nabla f(x)$ for the smooth function $f(x)$, and a proximal operator of $g(x)$, defined by

$$\text{prox}_{\lambda g}(z) = \arg \min_x \left(g(x) + \frac{1}{2\lambda} \|x - z\|^2 \right), \quad (5.3)$$

where λ is a scaling parameter [1]. Often $g(x)$ is selected to make computing (5.3) highly efficient. The solution x^* that minimizes (5.2), as obtained by the APG algorithm, is achieved by performing successive updates of $x^{(k)}$ and $z^{(k)}$ (see [1], [2]). The updates at each iteration are

$$z^{(k)} := x^{(k)} + c_k (x^{(k)} - x^{(k-1)}) \quad (5.4a)$$

$$x^{(k+1)} := \text{prox}_g \left(z^{(k)} - \beta^{-1} \nabla f(z^{(k)}) \right). \quad (5.4b)$$

The coefficient $c_k = (k-1)/(k+2)$ is a function of the iteration number k . The Lipschitz constant β corresponds to the maximum eigenvalue of $\nabla f(x)$. Limiting the gain of each iteration to β^{-1} ensures that the iterations remain bounded and will converge [2].

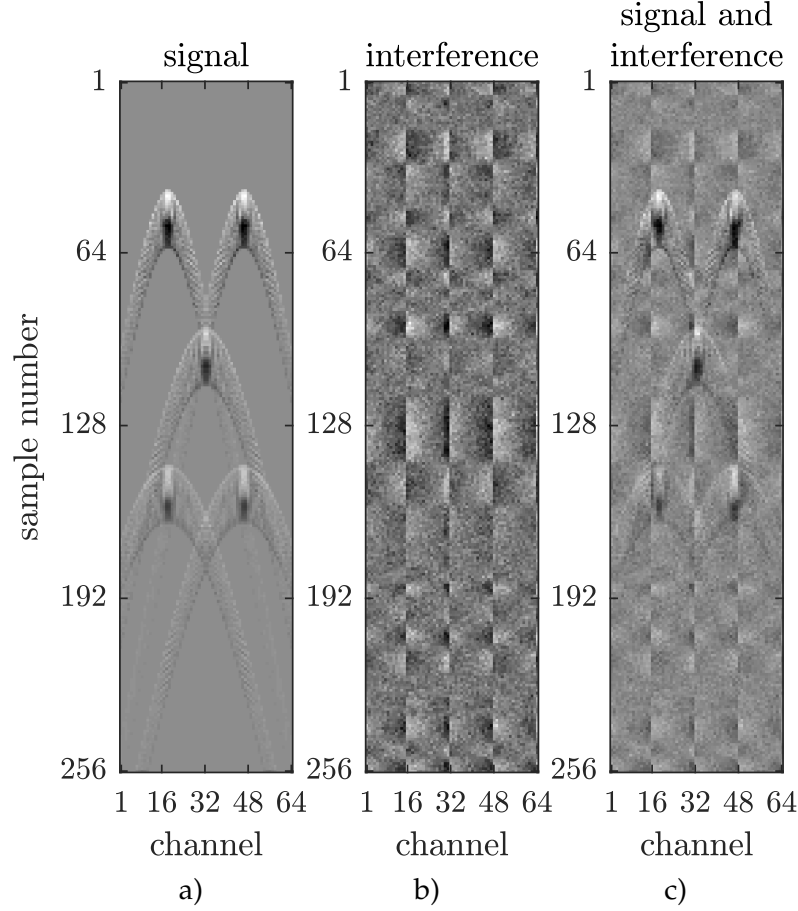


Figure 5.1: Simulated data measurements arranged as a matrix. a) Simulated signal produced by a digital phantom with 5 circular targets of diameter 2mm. b) Simulated interference consisting of white noise plus rank-1 EMI. It contains a time domain signal coupled by varying amounts to each channel. c) Signal plus interference used as input data matrix B .

5.4 REFORMULATED PROBLEM

To implement the proposed approach using the APG method, equation (5.1) must be written in the form of equation (5.2). The first term of (5.1) is $\|Hx - y\|_2^2$. Notice that this is a function of both x and y . Since $y = \text{vec}(B - P)$, it depends on the matrix $P = uv^T$, which is an unknown. We can also write $y = b - p$, where $p = \text{vec}(P) = \text{vec}(uv^T)$ and $b = \text{vec}(B)$. Therefore, the term can be rewritten as

$$\begin{aligned}
 f\left(\begin{bmatrix} x \\ p \end{bmatrix}\right) &= \|Hx - y\|_2^2 \\
 &= \|Hx - (b - p)\|_2^2 \\
 &= \left\| \begin{bmatrix} H & I \end{bmatrix} \begin{bmatrix} x \\ p \end{bmatrix} - b \right\|_2^2
 \end{aligned} \tag{5.5}$$

to fit the form of (5.2). In this representation, the unknown vector $\begin{bmatrix} x \\ p \end{bmatrix}$, which must be solved, is mixed between an image domain variable x and a data domain variable p .

From (5.5), the gradient of f is

$$\nabla f \left(\begin{bmatrix} x \\ p \end{bmatrix} \right) = 2 \begin{bmatrix} H^T H & H^T \\ H & I \end{bmatrix} \begin{bmatrix} x \\ p \end{bmatrix} - \begin{bmatrix} 2H^T b \\ 2b \end{bmatrix}. \quad (5.6)$$

It is convenient to write $P \equiv \text{vec}^{-1}(p)$, where vec^{-1} is inverse vectorization, which reshapes a vector to a matrix. Vectorization is a linear operation that is only a notational reshuffling, so it requires no computation beyond keeping track of indices when converting between vector p and matrix P .

The remaining term of (5.1) can be represented by g , where

$$g \left(\begin{bmatrix} x \\ p \end{bmatrix} \right) = \alpha_1 \Phi(x) + \alpha_2 \phi_{B,1}(P). \quad (5.7)$$

Here, the objective function for a rank- r approximation of P closest to B is represented by

$$\phi_{B,r}(P) = \|B - P\|_F^2 + \chi_{\text{rank} \leq r}(P), \quad (5.8)$$

where $\chi_{\text{rank} \leq r}(P)$ is the indicator function for a matrix of rank less than or equal to r . The indicator function is equal to zero if the rank condition is met, or infinity otherwise. The proximal operator for $\phi_{B,r}$ (see [26]) is provided below.

Equation (5.7) is separable in x and p . This means that the proximal operator is also separable (c.f. [1, Equation 2.1]). Therefore,

$$\text{prox}_g \left(\begin{bmatrix} x \\ p \end{bmatrix} \right) = \begin{bmatrix} \text{prox}_{\alpha_1 \Phi}(x) \\ \text{prox}_{\alpha_2 \phi_{B,1}}(P) \end{bmatrix}. \quad (5.9)$$

Observe that (5.9) describes a mixed-domain proximal operator. This can be used with ∇f from (5.6) to implement the APG updates using (5.4).

In (5.9), the operator $\text{prox}_{\alpha_1 \Phi}(x)$ can be computed with (5.3) by standard methods (see [1]–[6]).

A proximal operator for equation (5.8) has recently been described by Grussler et al. (2016) [26, Equation 22]. This operator can be written

$$\text{prox}_{\alpha \phi_{B,r}}(P) = \frac{1}{1 + \alpha} \text{SVD}_r(\alpha B + P), \quad (5.10)$$

where SVD_r is the rank- r approximation obtained with truncated SVD. Equation (5.10) can be computed quickly because a full SVD is not required.

To obtain a rank constrained matrix, (5.10) has an advantage over the proximal operator for nuclear norm minimization, which would also yield a low rank matrix (e.g., see [4], [27]–[29]). However, proximal updates for nuclear norm minimization are based on singular value thresholding, so rank of the resulting matrix is not easily known in advance by a particular choice of thresholding parameter.

5.5 IMPLEMENTATION

Equation (5.1) is implemented to reconstruct images for an opto-acoustic imaging system. Opto-acoustic imaging is a new modality that is currently being investigated for cancer diagnosis in clinical studies [8]–[10].

Here, the forward system matrix H represents the acoustic response of a volume to a wide-beam instantaneous laser pulse (i.e., the entire volume is illuminated simultaneously). Each voxel in the image volume corresponds to a source of acoustic pressure that is proportional to its optical absorption coefficient. From each source, an acoustic wave propagates radially outward at a known constant speed of sound. Acoustic signals are measured at the surface of the volume by ultrasonic transducers. The acoustic signal at any position and time is calculated as a superposition of waves arriving from each source. Thus, $y = Hx$ is the predicted measurement vector corresponding to an input vector x . For this implementation, $H \in \mathbb{R}^{(N_s M) \times (N_x N_y N_z)}$ is represented by a sparse matrix that corresponds to a linearized and discretized analytic equation. This is derived from solving the acoustic wave equation with heating source term (see [11], [21], [30, Chapter 7]). The predicted measurements (corresponding to Hx), are modelled by

$$\int_{\mathbb{R}^3} h(\mathbf{r}_i - \mathbf{r}, t) \tilde{x}(\mathbf{r}) d^3\mathbf{r}, \quad (5.11a)$$

at time t for each sensor position $\mathbf{r}_i$, with $i = 1 \dots M$. The function $\tilde{x}(\mathbf{r})$ is the opto-acoustic source distribution (corresponding to input vector x). The spatio-temporal impulse response (corresponding to H), which is applied with a different spatial offset for each sensor, is

$$h(\mathbf{r}, t) = \frac{\partial}{\partial t} \frac{\delta(\|\mathbf{r}\| - ct)}{4\pi t}, \quad (5.11b)$$

where $\delta(t)$ is the Dirac impulse, and c is the speed of sound.

A 2D digital phantom consisting of 5 targets was constructed to test this approach (illustrated in Figure 5.2a). The phantom was 20mm x 30mm, and the size in pixels is $(N_x, N_y, N_z) = (300, 200, 1)$. Each target is a circle with a diameter of 2mm. Signal data corresponding to the digital phantom was produced numerically from (5.11) for 64 transducer channels with 256 samples in each channel. Simulated EMI, consisting of white noise plus rank-1 interference, was added to the simulated signal data, as shown in Figure 5.1. Acoustic noise and optical photon noise, which would have different noise distributions, were assumed to be low compared to the EMI for this analysis, so they are not modelled.

To solve equation (5.1) and determine an image that best fits the data, equation (5.4) is used to implement the APG updates in Matlab as a main loop. The smooth function gradient ∇f is implemented by (5.6). The Lipschitz constant β is computed by determining the maximum eigenvalue of the augmented forward matrix, i.e., $\beta = \lambda_{\max}([H \ I])^2$. The proximal operator is implemented by (5.9) which separates into two parts. To compute (5.10), only the principal eigenvectors need to be evaluated, which is done using a truncated SVD. The approach of Beck et al. (2009) [6] is used to implement $\text{prox}_{\Phi_{\text{TV}}}(x)$ for isotropic TV regularization in the image domain.

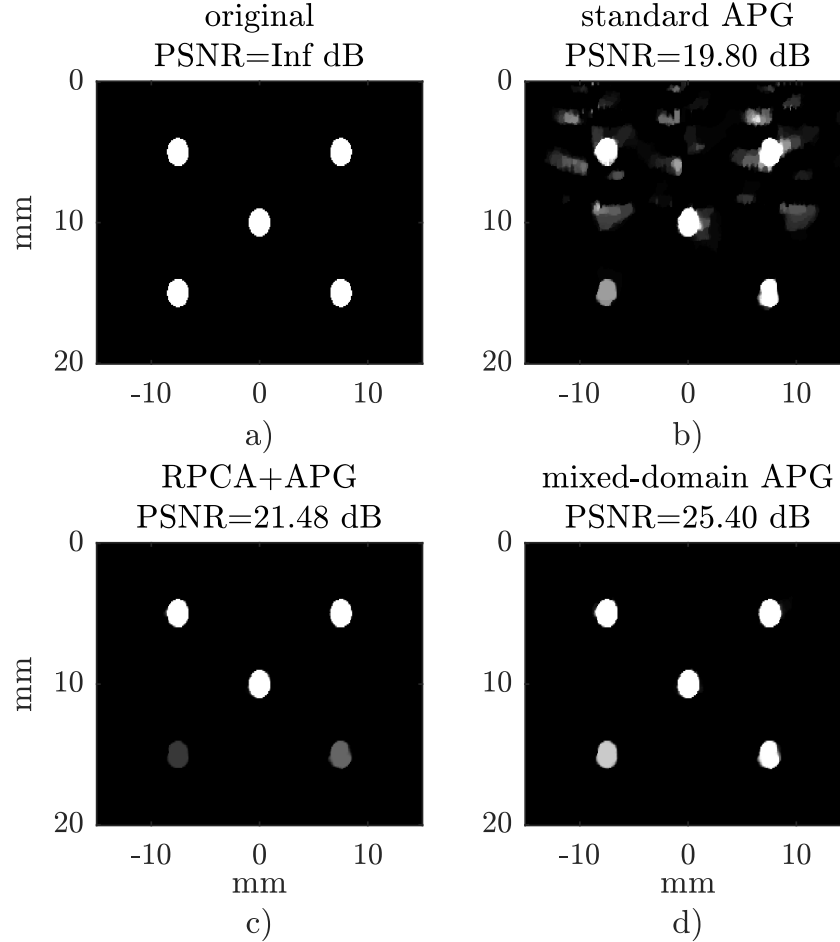


Figure 5.2: Results compared in image domain. a) Original target configuration corresponding to interference-free data of Figure 5.1a. Images reconstructed from signal plus interference data of Figure 5.1c using b) standard APG algorithm, c) RPCA+APG algorithm and d) mixed-domain APG algorithm.

5.6 RESULTS

In Section IV, a mathematical formulation for performing EMI removal with a mixed-domain APG algorithm was presented. Results are now compared against two other approaches. First, a standard APG algorithm of Section III [1]–[6] is used without including any EMI removal (Figure 5.2b). Second, pre-processing with RPCA [18] is used to filter the EMI (Figure 5.2c). Figure 5.2d demonstrates the mixed-domain APG approach. For reference, Figure 5.2a shows the original target configuration, corresponding to a perfect reconstruction. All reconstructions used the input data of Figure 5.1c. The input data contained interference consisting of white noise plus a rank-1 coupled EMI interference pattern. Output is shown after 100 iterations, with PSNR values indicated for each case. When the standard APG algorithm (without EMI removal) was applied, the reconstruction contained artifacts due to the rank-1 interference, and had low PSNR, as apparent in Figure 5.2b. The RPCA algorithm separates a matrix into low-rank plus sparse components, so valid signal corresponds to the sparse component. This makes it most well suited

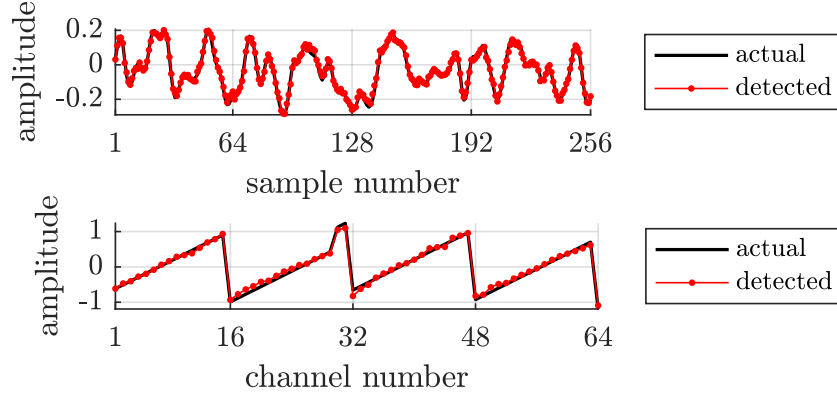


Figure 5.3: EMI signal extracted after algorithm completion. The detected EMI signal is compared to the actual true value. (top) the vector u corresponds to the time dependent common noise. (bottom) the vector v corresponds to the amount of noise coupled to each channel.

to remove rank-1 EMI from input data, compared to other pre-processing approaches described in Section I. However, when signal is weak compared to the noise level, as is the case with the deeper targets, the RPCA tends to remove some valid signal as well, as seen in Figure 5.2c. If the noise level is raised further, the deep targets fully disappear. The mixed-domain APG approach avoids this problem by performing regularization in the image domain, which improves performance for weak signals. As seen in Figure 5.2d, this results in higher a PSNR compared to pre-filtering with RPCA. Figure 5.3 shows the EMI extracted by the mixed-domain algorithm. The synthetic dataset used here was selected for conceptually illustrating the technique. A full performance analysis to assess PSNR effectiveness on multiple datasets is beyond the scope of this paper.

The mixed-domain APG is slightly slower than the standard APG due to computing an additional rank-1 SVD at each iteration. The theoretical convergence rate for APG is $\mathcal{O}(1/k^2)$ [6], [7]. Convergence for all three methods in Figure 5.2 was found to be similar in each case, consistent with the theoretical APG convergence until plateau is reached. For the existing parameters, at beyond approximately 60 iterations, additional improvements to the objective function were very small and were not visually noticeable.

5.7 CONCLUSION

An approach was presented that is able to separate valid signal from EMI concurrently during image reconstruction. To solve unknown variables that are mixed between the image and data domains, modified APG updates of equation (5.4) were proposed. This involved using equation (5.6) as the smooth function gradient ∇f and using equation (5.9) for the mixed proximal operator prox_g .

This may have use in imaging systems where EMI is correlated across multiple channels, or where structure is present in mixed domains.

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This dissertation developed methods to improve OA image reconstruction and device characterization for systems that use a linear-array probe. The theory and techniques of Chapters 2 through 5 represent the significant contributions resulting from this work. This includes methods for device characterization (Chapter 2), rapid and realistic OA simulation (Chapter 3), multi-frame image reconstruction using convex optimization algorithms (Chapter 4), and interference suppression using convex optimization algorithms (Chapter 5). The hypothesis of this dissertation (Section 1.2) is that image reconstruction can be improved with convex mathematical optimization using data collected at multiple probe positions. This was analyzed using phantoms to compare the proposed techniques with formula-based analytic reconstruction.

In Chapter 2, the specific aim was to develop methods for characterizing OA imaging systems. Evaluating the ability to display s_{O_2} and c_{tHb} presented a challenge because the clinical system that was investigated used a novel visualization technique based on statistical color mapping [1], [2], which had not previously been characterized. In addition, the system described in Chapter 2 uses an analytic formula-based approach for image reconstruction [1], [2], which permitted the acquired datasets be used as a baseline for comparing methods developed in Chapter 4. In Chapter 2, a phantom consisting of two vessels at independently controlled oxygenation levels was constructed that enables sufficient parameter variation to permit characterization. Novel image quality metrics were proposed to quantify the statistically mapped image colorization and the displayed image contrast (Section 2.3.3). These metrics were used to evaluate performance at different depth and hematocrit levels (Figures 2.8, 2.10, 2.11 and 2.13). Chapter 2 showed that it is possible to characterize the visualization of statistically-mapped relative s_{O_2} and c_{tHb} , which is an interesting result because quantitative molecular concentrations are not measured or displayed by the device being characterized (see Section 2.5.6). Previous methods of device characterization [3] have instead focused on evaluating quantitative s_{O_2} levels for clinical OA assessment, rather than relative s_{O_2} levels. Accordingly, by revealing how statistical color mapping behaves as the imaging depth and hematocrit levels are varied, the characterization techniques developed in Chapter 2 provide information that may facilitate the clinical interpretation and assessment of benign and malignant lesions in tissue.

In Chapter 3, methods to simulate OA signals from a 3D volume were developed. The specific aim was to achieve rapid computational performance for simulating a linear-array with realistic transducer elements, suitable for solving an inverse problem. A separable computational model was formulated in the time-domain. When used with a linear-array, the separable model permits an order-of-magnitude computational improvement compared to a non-separable model. For a

3D volume with n^3 voxels, acceleration by a factor of n was demonstrated. A main advantage of the proposed formulation is its applicability towards iterative image reconstruction, which alleviates a performance bottleneck that arises because the forward simulation operator (and its adjoint) must be computed many times to form an image (as described in Chapter 4). The theory and mathematical proofs developed in Chapter 3 provide a framework that is flexible for developing image reconstruction approaches. This is partly because the developed mathematical notation facilitates manipulating continuous equations (used for acoustic waves) as well as linear matrix operators (used for reconstruction). Consequently, illumination and probe position can be modeled effectively for both 2D and 3D systems. Moreover, the modeled linear-array geometry provides the ability to simulate signals pertaining to the clinical system described in Chapter 2, which is an important aspect of this research. However, the formulation in Chapter 3 only deals with single-wavelength illumination, not multiple wavelengths, which are critical for determining s_{O_2} . Furthermore, the scope of Chapter 3 was limited to simulation, and does not implement or provide details about reconstruction. The theory of Chapter 3 was subsequently used in Chapter 4, where it was adapted to multiple optical wavelengths and incorporated into an inverse problem for reconstruction.

Chapter 4 addressed the main topic of this dissertation: 3D image reconstruction and motion tracking with convex optimization. Novel techniques were proposed that had not been previously attempted. Images reconstructed with the proposed techniques were compared to a formula-based analytic approach. Data and images from the phantom described in Chapter 2 were used to evaluate contrast-to-background ratio (CBR) as a function of depth (Figure 4.S.8). The analysis of Section 4.S.2 shows that the proposed approach can achieve a significantly higher CBR, compared to the formula-based approach, until a noise-floor limit is reached. This supports the hypothesis that image quality can be improved by the proposed techniques. However, although a significant improvement was demonstrated, one limitation of this comparison is that it does not address whether a different analytic approach (other than the one used in Chapter 2) could have achieved a better result from the same data. As mentioned in Section 4.S.2, when acoustic signals are weak compared to background, reconstruction with convex optimization may filter out such content. Nevertheless, when signal intensity is strong, convex optimization was shown effective at reducing background interference, and at suppressing “streak” artifact that resulted from point-spread in analytic reconstructions. This significantly improves CBR. Formula-based analytic approaches do not have similar mechanisms to eliminate background interference. Therefore, the CBR of analytic approaches will tend to be lower, provided that signal strength is above an implementation-dependent threshold that optimization-based regularization filters out. In Chapter 4, digital phantoms were also used to test the hypothesis. Section 4.S.3 compared reconstruction for a phantom consisting of two spherical targets, and demonstrated that out-of-plane artifact suppression improves with convex optimization compared to analytic back-projection. The number of frames was varied to evaluate the effect of using multiple frames. In

Section 4.S.3, it was shown that when multiple frames are used, the image quality performance is improved. These results further support the hypothesis that image quality improves when multiple frames are used in reconstruction.

In Chapter 4, a clinically acquired dataset of a benign breast lesion was reconstructed using the proposed techniques (see Section 4.5.3). Figure 4.7 compares the results of dual-wavelength multi-frame optimization-based reconstruction to analytic back-projection. The results demonstrate enhanced visualization of vascular structures within the lesion. In Figure 4.7, statistical color mapping was used to overlay OA data with conventional grayscale ultrasound. Using the optimization-based technique, the capsular vessels surrounding the lesion reconstruct with significantly reduced artifact compared to the backprojection-based approach. This is because the proposed technique improves acoustic source localization of the vessels, which helps to suppress streak artifact and out-of-plane artifact that contribute to clutter. This suppresses noise that would otherwise fill the background, which enhances contrast of the vessels.

While the focus of Chapter 4 is on 3D image reconstruction, 2D reconstruction is a special case of this, where only a thin slice of the volume is required. Interestingly, modeling of 2D imaging, when stored in memory as a 3D volume, can facilitate artifact suppression. In fact, using 3D geometry permits regularized deconvolution with the transducer's 3D spatio-temporal impulse response, even for the single-frame case (Section 4.S.3). Moreover, with a single frame of OA data, modeling of wide transducer elements was shown to better localize out-of-plane artifact in a 3D volume compared to using ideal transducer elements (see Section 4.S.3/Figures 4.S.13 to 4.S.15). When using multiple frames, the ability to localize and suppress out-of-plane sources improved compared to using single frames (Section 4.S.3/Figures 4.S.13 to 4.S.16). Using the 3D model helps infer direction-of-arrival to suppress out-of-plane signals. Interestingly, because the mathematical operators defined in Chapter 3 are separable, when performing single-frame reconstruction, a 3D volume with n^3 voxels can be reconstructed using constant-order $\mathcal{O}(1)$ computational overhead compared to 2D reconstruction (i.e., by using two $\mathcal{O}(n^2)$ operators instead of one), which only requires additional memory to store the 3D volume. Also, by applying a regularization function to each voxel, regularization can be performed on the 3D volume with $\mathcal{O}(n^3)$ complexity, as compared to $\mathcal{O}(n^2)$ for a 2D volume. This means the 3D methods developed in Chapter 4 can be applied to 2D imaging without significant computational overhead. Real-time implementation of optimization-based 2D and 3D reconstruction, which involves rapidly producing images of subjects as they are scanned, is a subject of future work.

There are several reasons why the reconstruction approach proposed in Chapter 4 is favorable compared to methods for freehand conventional ultrasound [4]–[12] that have previously been studied. First, although OA and ultrasound both involve acoustic waves, OA contains certain types of interference that are significantly different from ultrasound. Compared to OA, the transmitted acoustic pulses and back-scattered echos used by ultrasound have a high center frequency with narrowband content. Consequently, in ultrasound, hardware such as directional transducers, or the presence of an acoustic lens, can be used to limit elevational resolution, confining transmitted and

received signals to the probe's imaging plane. However, in OA, signals have broadband acoustic frequency content, which limits the potential to reject out-of-plane interference with such hardware adaptations. In addition, to improve image quality, ultrasound uses spatial compounding, which forms images by sending multiple transmit pulses with different focus or beam angles. However, in OA, there is limited ability to control the light distribution to provide independent views of tissue without moving the probe, so spatial compounding is not generally applicable. This leads to higher clutter in OA, and is one reason why this dissertation studied multiple acquisitions of a moving probe. Furthermore, light attenuates in tissue more rapidly than sound, so the penetration depth of ultrasound is greater than in OA, and can improve in OA with multiple acquisitions. Lastly, ultrasound images contain speckle, resulting from constructive and destructive wave interference produced by sub-resolution acoustic sources that directionally scatter the transmitted wavefront. For various reasons, including that OA has broadband frequency content, and that OA absorbers simultaneously emit omni-directional acoustic waves, speckle interference does not occur as strongly in OA images [13].

The notation in Chapter 3 includes 3D spatial convolution with an aperture function (Equation 3.11). This yields an exact analytic expression for the OA transducer's spatio-temporal impulse response, and each spatial position has a different temporal response. In ultrasound, although exact expressions for the standalone transmit or standalone receive responses can be computed in a similar manner [14], care must be taken for the overall ultrasound scatterer response, which involves a temporal convolution of its transmit and receive responses and depends on the transmitter and receiver positions. Convolution of the ultrasound response with a spatial aperture implicitly yields an approximation (transmit and receive distances are assumed locally constant), which holds true only for small apertures. In OA, this is not a problem because light is assumed to propagate instantaneously, so there are no transmit delays. This preserves the spatial convolution properties, so the OA computation is exact.

Chapter 4 proposed a technique to automatically determine the motion of an OA probe without using external sensors, while simultaneously performing 3D reconstruction. Using a digital phantom, it is demonstrated in Section 4.5.2 that this approach can be used to estimate elevational probe motion. As described in Section 4.6, because OA does not have similar image speckle or elevational resolution to conventional ultrasound, techniques to determine elevational motion that are used in ultrasound [4]–[12] are not generally applicable in OA. Specifically, when using a linear-array OA probe, since the transducer elements are arranged co-linearly, it can be difficult to determine elevational motion. On the other hand, the lateral motion of the OA probe (along the array axis) can easily be determined using correlation-based approaches because the motion manifests as horizontal translation in the reconstructed 2D imaging plane. An advantage of the technique proposed in Chapter 4 is that out-of-plane OA sources may provide targets for motion tracking to “lock onto”, which can be used to improve elevational motion tracking (Section 4.6). In Chapter 4, the analysis was limited to elevational motion tracking (Section 4.5.2). However, the proposed approach is applicable towards estimating general probe motion of an

arbitrary trajectory, which is the subject of future work. Moreover, since an arbitrary trajectory can be approximated as a sequence of linear segments, decomposition approaches involving segments of linear trajectories can be investigated in future work to improve performance.

An important aspect of the model in Chapter 4 is that it applies to multi-wavelength reconstruction, which can determine volume fractions of molecular tissue chromophores. For this reason, Chapter 4 directly relates to the s_{O_2} visualization described in Chapter 2. Multi-wavelength reconstruction is demonstrated in Chapter 4 (Figures 4.4 and 4.5), where results show distinction of reconstructed chromophores using relative colorization. Future work involves using the methods of Chapter 4 to evaluate quantitative chromophore concentrations.

The illumination model proposed in Chapters 3 and 4 permits more accurate quantitative evaluation, compared to simplistic illumination models. However, one limitation is that this illumination model does not change with respect to tissue composition because it uses a pre-computed fluence distribution, which is a reasonable approximation for optically homogeneous breast tissue. A subject of future work would be to include adaptive illumination models (possibly iteratively), where illumination is continually updated as tissue composition is solved. In this manner, dynamically applying illumination based on tissue properties could potentially improve performance for quantitative imaging.

Chapter 5 combines OA reconstruction with interference suppression. The proposed approach used an electromagnetic interference (EMI) model with a system response for 2D OA imaging. For image reconstruction, a convex optimization term representing the EMI model was added to the minimized objective function (Equation 5.1). The system response used in Chapter 5 is simpler than what is used in Chapter 4, because it is limited to a single-wavelength 2D case. Results demonstrated an improved PSNR compared to other methods. A topic for future work is to combine the EMI interference term with the objective function of Chapter 4 for multi-wavelength 3D reconstruction.

In conclusion, this dissertation involved developing several techniques [2], [15]–[17] with potential application towards enhanced visualization of vascular structures in tissue, useful for diagnosis and detection of cancer and other diseases. Computational improvements were obtained that permit faster and more accurate models for OA image reconstruction, overcoming several limitations of previous techniques. Future work involves deploying these methods in real-time OA imaging systems.

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