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3D volumetric mapping of tissue properties
via a catheter-scale microendoscope imaging system

An Undergraduate Honors College Thesis

In the

Department of Biomedical Engineering

College of Engineering

University of Arkansas

Fayetteville, AR

By

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3D volumetric mapping of tissue properties via a catheter-scale microendoscope imaging system

Abstract

The study of tumor microvasculature is an important area of interest for research and clinical communities; however, there are significant limitations in the clinical characterization of the tumor microenvironment. Optical methods offer quantitative real-time measurement of tissue structure and perfusion and can be miniaturized for deployment endoscopically into previously inaccessible locations. However, conventional optical methods (i.e., optical coherence tomography, white light endoscopy, etc.) gives limited information about tissue perfusion while the diameter of various optical probes along with the complexity of scanning mechanisms make it difficult to access certain areas. In this study, a new technique for characterizing the tumor microenvironment is presented; Utilizing photon depth penetration information calculated via Monte Carlo simulations along with 2D image data from a phantom-based model, an absorber that lies beneath the surface can be approximated by a point cloud. Being able to approximate an absorber beneath the surface is key in locating important tissue components in practice and would be able to give clinicians a better look at what is happening. To accomplish this, Simulations modeled forward photon transport of a beam of light starting from a source fiber going through tissue and then exiting at the image guide at a variety of different exit positions. These simulations were created with predetermined optical properties based on colon epithelium. This data was then used in conjunction with depth approximations and absorber data obtained through a point cloud system to yield an approximation of an absorber below tissue. Point cloud maps of an estimated absorber were able to be created; however, in the future, they can be refined using multiple source fibers situated around the probe to create multiple projections from different sides.

Introduction

The study of tissue microvasculature within the microenvironment during tumor development is an emerging area of interest for research and clinical communities. Basic knowledge of tumor vasculature has led to promising anti-angiogenic therapies as well as improving our understanding of the interactions between tumor cells and extracellular components¹. There are a number of methods for *in vivo* assessment of the tissue microenvironment that can be applied to a range of anatomic locations. Optical methods offer quantitative real-time measurements of tissue structure and perfusion. These optical methods typically use one of two light and scattering interaction regimes. Signal scattering events, where photons undergo a single scattering event, are commonly used in high-resolution imaging systems such as confocal microscopy, multi-photon microscopy, and optical coherence tomography. Although these methods provide good spatial resolution and superior depth penetration, these methods yield limited information about tissue perfusion, and the complexity of these methods makes it difficult to access various anatomical locations, such as the colon epithelium *in vivo*. Diffuse scattering regimes rely on numerous scattering events within tissue and feature widely spaced illumination sources and detectors. These widely spaced illumination sources and detectors are typically much greater than one reduced mean-free path in order to work due to the radiative transfer equation, preventing it from being used to image places that require small instruments. Near infrared spectroscopy (NIRS) and diffuse optical tomography offer excellent depth penetration and can quantify functional changes within the tissue (i.e., hemoglobin, oxygen saturation, and lipid content). However, these methods are limited and cannot resolve fine vascular or structural details, and typically require large source-detector separations, making deployment endoscopically impossible.

Microendoscopy is a classification of endoscopy that uses a catheter-sized probe that utilizes optical fibers to image tissues on a small scale for better analysis of the tissue of interest. Fiber-optical microendoscopy has led to innovations in imaging of freely moving animals, long-term imaging, minimally invasive diagnostics, and microsurgery⁴. We have previously developed an optical fiber bundle image guide-based microendoscopy platform that comprises of a flexible fiber optic image guide bundle along with source fibers surrounding the image guide fiber (**Figure 1-1**). Briefly, one source fiber emits light that diffuses and reflects through the tissue of interest, which is then captured by the image guide and creates an image that depicts the tissue surface.

However, conventional widefield microendoscopy platforms fail to quantify what is happening beneath the surface of tissue since it is constrained to the superficial layer of tissue which relies on exogenous fluorescence contrast. Conventional microendoscopy platforms are necessarily diameter-restricted, which means that any remitted scattered light has only undergone a few scattering events, and the diffuse approximation of light is no longer valid. Conventional diffuse optical tomography-based image reconstruction methods are also inaccurate at this length scale and alternative methods for image reconstruction must be used. To combat these limitations, a multimodal, multi-projection tomographic microendoscopy system can be created. Tomographic three-dimensional reconstruction of absorption or fluorescence data is possible using a fiber bundle microendoscopy architecture by spatial mapping of surface fluence, captured via a fiber bundle. This approach uses photon trajectories and depth information of the tissue in conjunction with 2D image probe data to create an approximation of various extremities in the tissue. These photon trajectories along with the associated photon depth information, photon propagation can be simulated via the Monte-Carlo method. Monte-Carlo modeling has been used frequently to simulate forward photon propagation in tissues which provides good accuracy and flexibility

compared with other theories² because simpler approximations of photon scattering cannot be performed (such as those used for diffuse scattering approaches over much larger distances). Monte-Carlo simulations software can be used to model photon transport coming out of a source fiber going through tissue and then exiting at the image guide at a variety of different exit positions as shown in **Figure 1-3**.

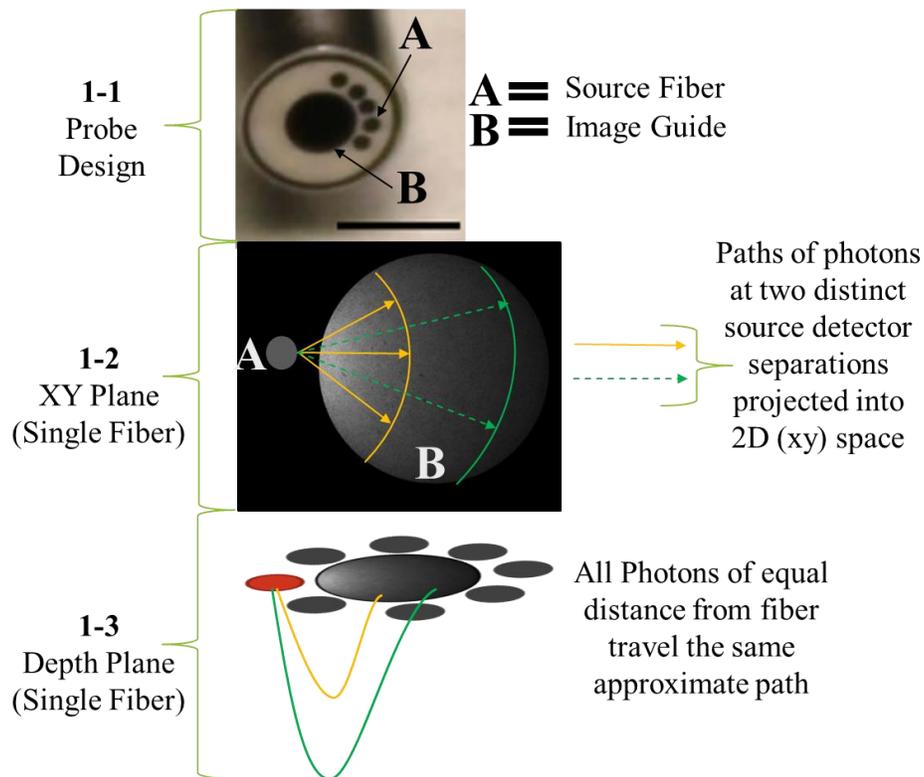


Figure 1-1. The front face of the probe. A represents one of the five source fibers with B representing the image guide. This probe represents the exit (image guide) and entrance (source fiber) points of the photons that will be mapped (Scale bar=2.5mm). Image taken from Greening. **Figure 1-2.** The image guide collects a real tissue image with light emitted from one source fiber and remitted back to the surface. Monte Carlo simulations represent the photon trajectories for a range of exit positions imaged by the fiber. In this case .5mm(yellow) and .9mm(green). It is important to note that all exit positions along a certain radius have the same average travel path. **Figure 1-3.** Represents the probe with source fiber(A) and the image guide(B)

with photon paths coming out of the active source fiber (shown in red) transporting through a tissue(C) and coming out along various exit positions on the optical guide. These exit positions and paths are simulated with Monte Carlo and Matlab.

In this study, we use Monte Carlo simulations and two-dimensional image data from a phantom-based model of the colon epithelium, based on previously reported optical properties to estimate the photon trajectories within the tissue to help estimate light absorption during diffuse scattering with the goal of estimating where an absorber lies beneath the surface along with mapping it's shape. Knowledge of where an absorber lies beneath the surface is instrumental to clinicians, who could use the technology to obtain tumor microvasculature information to develop patient-specific drug regimens along with a myriad of other things. The photon path curves obtained from the Monte Carlo simulations were used to obtain depth data about photon tissue penetration for a particular Source Detector Separation. Absorbers were estimated below surfaces for hypothetical shadows along with a probe image by overlapping photon path curves, allowing for a point cloud to be created estimating the absorber's location. These point clouds would also be refined using multiple projections from different source fibers allowing for greater accuracy. These findings illustrate the feasibility of the proposed method through future development and study.

Materials and Methods

I. Monte Carlo Simulations of photon propagation as a function of depth

To simulate forward photon propagation through tissue, Monte Carlo software² was used. More specifically, to simulate colon epithelium, a range of predetermined dimensions and optical properties were used³. In the simulations we used the following values from **Table 1**.

Table 1. Representative optical properties used in Monte Carlo models

Absorption Coefficient (μ_a)	1cm^{-1}
Scattering Coefficient (μ_s)	20cm^{-1}
Anisotropy (g)	0.9
Number Of Photons	4.5×10^6
Tissue Geometry	2x2x2mm

The Absorption coefficient of 1cm^{-1} was chosen because this is the lower bound of biological tissue^{5,7} (0-10 cm^{-1}). The Scattering coefficient of 20cm^{-1} was chosen because this is close to the upper bound of biological tissue^{5,7} (5-26 cm^{-1}). The Anisotropy value was chosen because 0.9 is the conventional anisotropic value that most accurately models biological tissue⁸. Tissue geometry was chosen at 2x2x2mm because this accurately contains the photon information needed since the max source-detector separation is 1.3 mm. 4.5×10^6 photons were used as this is close to the limit MATLAB would allow while having a low amount of noise.

These simulations traced individual photon paths emitted from a source fiber and captured by an image guide. Individual photon paths were collected into a .txt file, then fed into a custom MATLAB code for analysis. First, the starting positions of each photon (0,0,0) were found. From here, each photon was separated into a single cell array. Any photons that traveled outside of the simulated tissue were filtered out. Then, looking at the end Z values for each photon, any photon that had a Z value > 0 was filtered out due to only wanting Z values that have a Z value of 0 since that means they were reflected. Next, the distance formula

$$d = \sqrt{(x^2 - x^1)^2 + (y^2 - y^1)^2}$$

was used to determine the distance traveled at each step of each photon. Then depending on the selected source-detector separation photons would be filtered out if they did not exit at the specified point (with a range of 0.01 mm). From here this data was discretized and accumulated into bins. Finally, the collection of photon paths was displayed as a histogram to represent the depth of photon diffusion through the tissue represented as the y-axis and the movement through the XY plane represented as the x-axis. The voxel size of this histogram was set at .01 mm in order to match the pixel size of the image output by the optical guide.

II. 3D Reconstruction of a Point Map based off the absorption and depth data

To create a point map, the Monte Carlo-based photon paths were fitted to a curve within MATLAB by finding the maximum value for each column of the photon path histogram. These Photon paths were generated in Method 1 and yielded a figure like Figure 2A. The color of the photon path curves is indicative of the number of photons that pass through that region. Since only the reflected photons were kept due to them being the only ones picked up by the image guide, the photon path histogram forms a “banana curve,” a standard histogram important in studying Monte Carlo simulation data. Only one exit position is calculated at a time due to the nature of what this study is trying to accomplish. To more accurately approximate where an absorber lies, each exit position across the image guide is calculated separately. Pixels/voxels that have the same source-detector separation only need to be generated once since they would have the same average photon path through the tissue of interest. After finding the maximum value for each column of the photon path histogram, the average for every two columns is determined and replaced with those values. This allows for a much smoother curve.

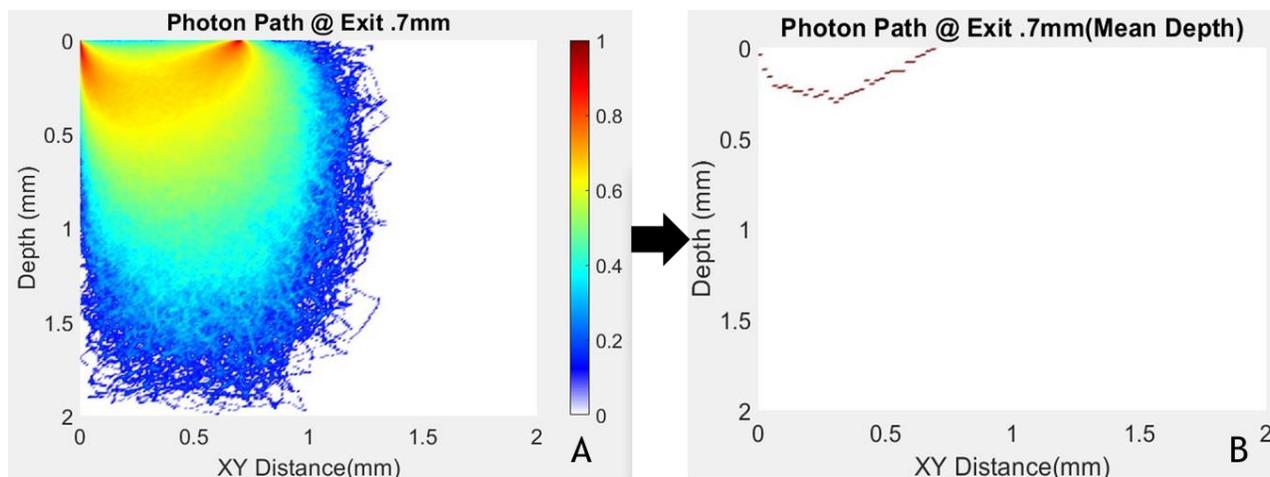


Figure 2. A) The photon trajectories are shown for a source detector separation of 0.7mm; however, this data is generated for all possible source detector separations **B)** Curve with data points illustrating the curve from A

From here, the data is taken and then for each point along the curve the distance between it and the surface is determined. From here a histogram vector is made with color corresponding to depth, illustrated in Figure 3B. This histogram vector represents a “birds-eye view” of depth, with color to show the depth at which an average photon would have to travel to exit at the shown exit position.

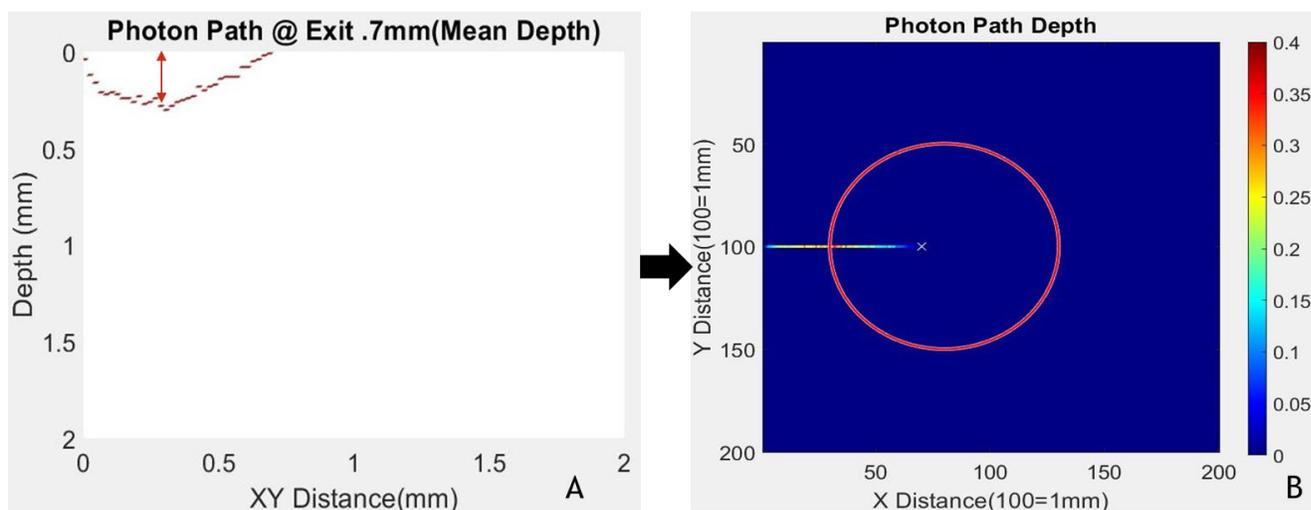


Figure 3. A) For each value along the XY axis only the max remains, allowing for the depth to be

calculated from this max value to the surface (Red arrow illustrates depth measurement) **B**) The depth vector colormap is shown with red meaning deepest and blue meaning shallowest. The red circle indicates the image guide.

Then a vector was made of the depth from the surface for each voxel contained within the image guide and stored. To better represent how these images compare to the images generated in Method 1, the figure depicted below was created.

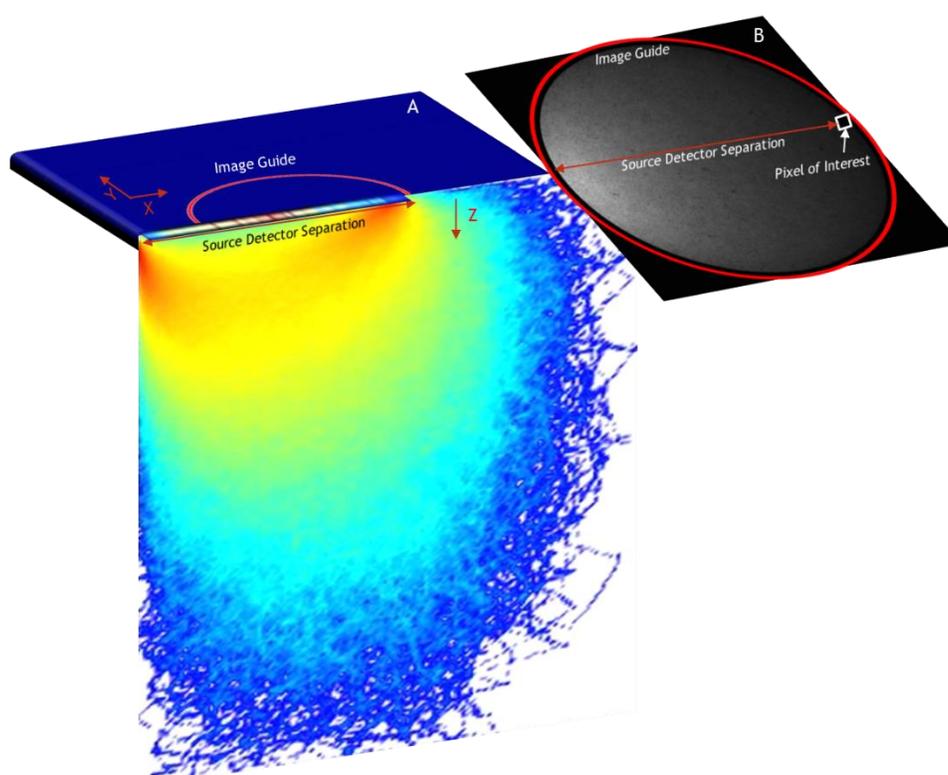


Figure 4. A) A visualization of the correlation of depth with surface absorption **B**) A visualization with a real output image with the respective pixel of interest (Red Circle indicates the image guide)

This method gave important information for a particular voxel contained within the image guide. In addition to the depth data, data was estimated for if there was an absorber placed below the surface that spanned multiple pixels of the output image. To better estimate where an absorber

lies, the photon paths of the photons exiting at those pixels are overlaid, with the parts of the paths that are similar illustrate where the absorber could lie within the 3D tissue of interest.

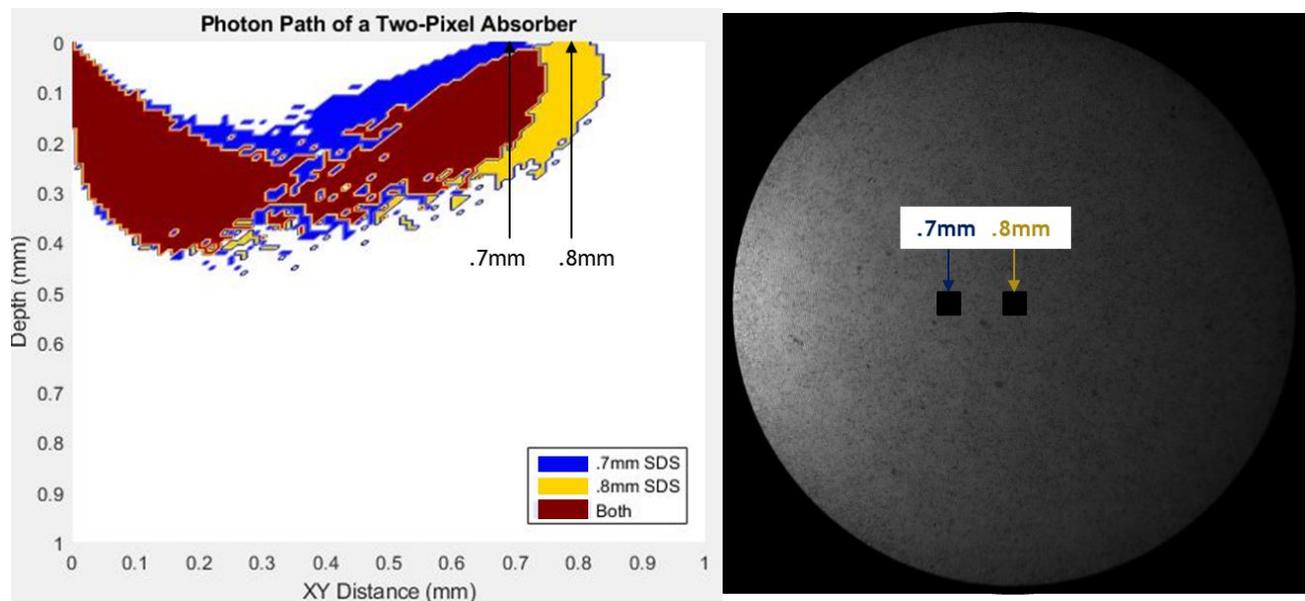


Figure 5. The photon trajectories are shown for a 2-pixel absorber with an exit range of .7-.71(Blue) and .8-.81(yellow). Red represents the regions where there is overlap. This point cloud illustrates where the absorber would most likely lie.

This process would then be repeated for each source fiber on the image probe (A total of 8). This allows for an even greater approximation of the absorber as there is now data from each source, refining the point cloud map further.

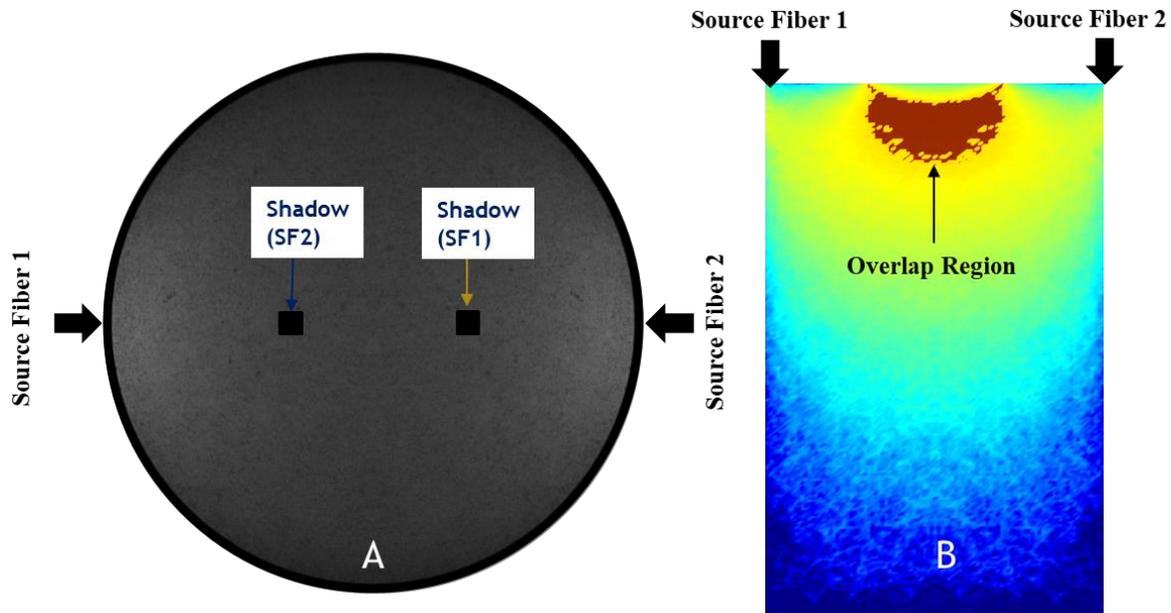


Figure 6 **A)** Two source fibers shown with their respective curves overlaid, each one showing a shadow of pixels **B)** Both fibers have a unique estimated photon curve, creating a point cloud of overlaid points generating an approximate cloud of where the absorber lies beneath the surface.

Results

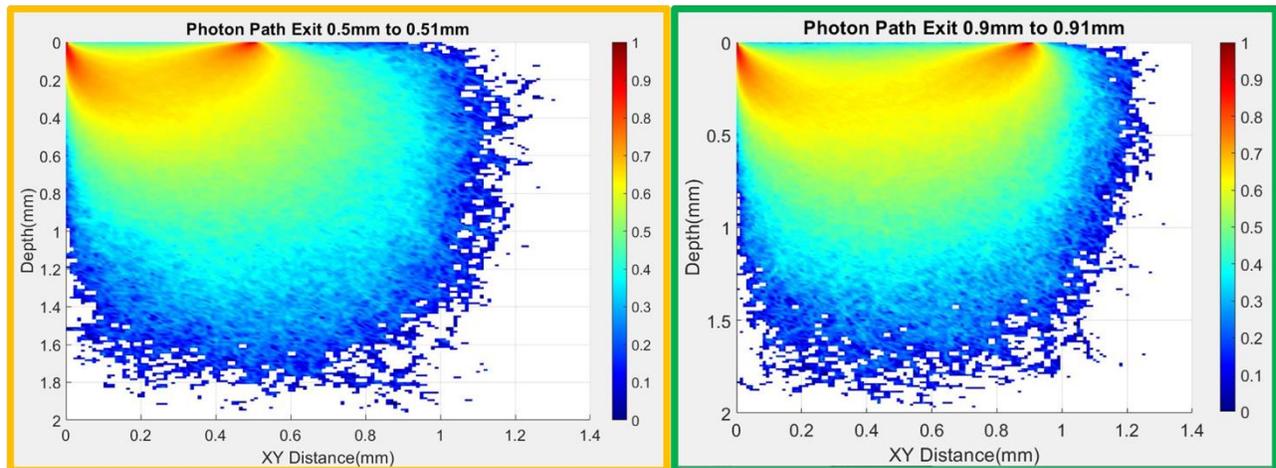
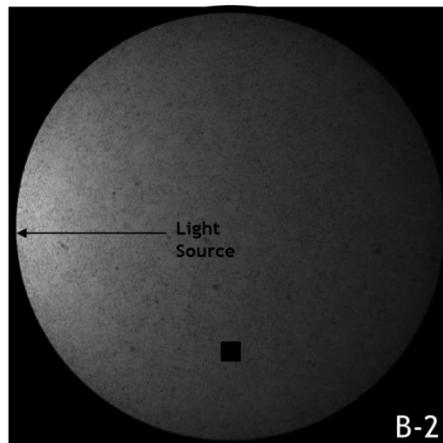
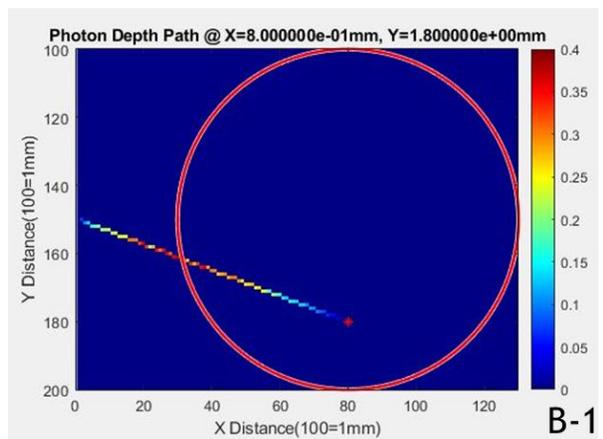
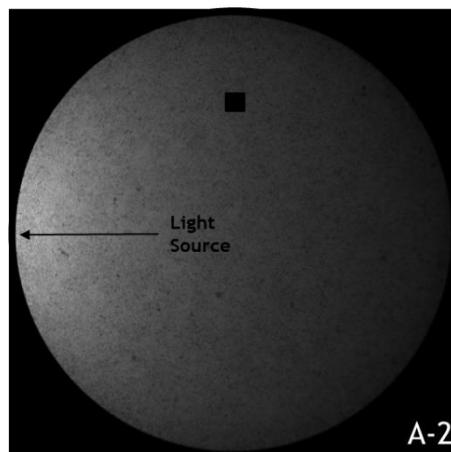
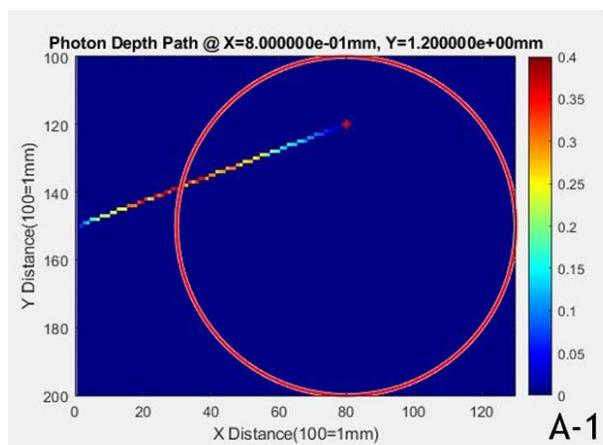


Figure 7. Simulated representations of photon paths with depth information and varying exit positions (0.5 mm to 0.51 mm(yellow) and 0.9 mm to 0.91 mm(green)) are depicted.

These photon curves were generated using the method previously described. The two depicted in Figure 7 are just a few of the curves generated. All possible source-detector separations between 0 and 1.3mm were generated and stored for later to be used in Method 2 where colorbar depth images were generated like the ones below.



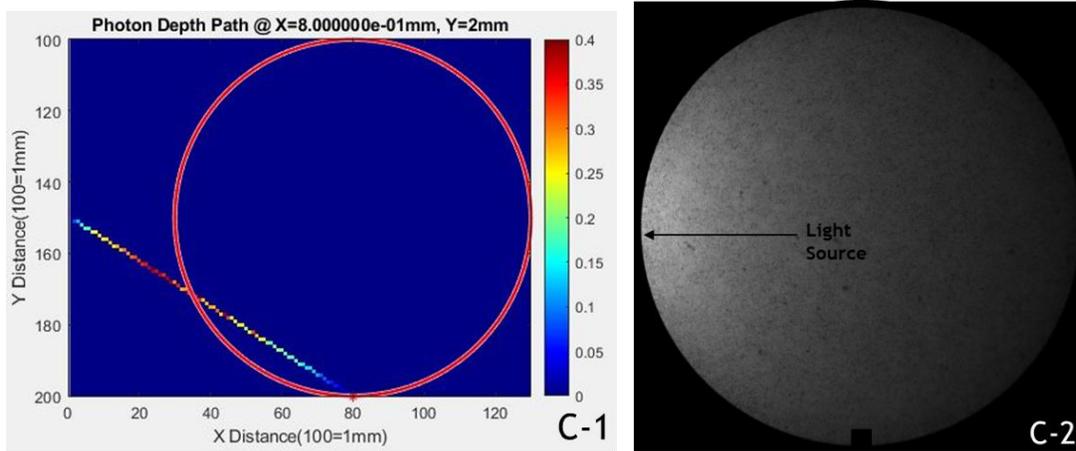


Figure 8. In figures A-1, B-1, and C-1, the depth map of 3 separate photon path curves is shown along the middle of the image guide (80mm from source fiber). Figures A-2, B-2, and C-2 show the corresponding image guide with the pixel absorber if it were present (absorber not to scale)

Discussion

The results successfully verify the methodology presented in Methods 1 and 2. Using Monte-Carlo simulations with known testing parameters (Method 1), It was shown that an absorber can be estimated underneath the surface using a point map-like system based on the estimated depth information of the photon paths that match an absorber beneath the surface (Method 2). In addition, it was shown that for a multiple pixel image where there is a shadow on the surface, the photon paths that overlap form a region where the absorber would most likely lie beneath the tissue of interest. However, there still stands for a certain degree of future work. Generating a point cloud for a singular pixel and two-pixel absorber has been shown in our methodology. To generate a more approximate point cloud, source fibers could be placed in a circle around the image guide to provide absorption data all around the absorber allowing for its location to be more accurately estimated beneath the surface. In addition, using photon intensity curves across the real image, the point cloud of the estimated absorber can be weighted based on how much the experimental photon

intensity curve deviates from the theoretical. In the near future, this technology could be used to approximate a generic absorber underneath a PDMS phantom using all 8 source fibers surrounding a recently designed probe (created in the lab) to map the absorber. This technique can then be further improved so that in the future it could map tumor microvasculature in an endoscopic device creating a map of where the tumor and its associated microvasculature are located.

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