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A capillary-mimicking optical tissue phantom for diffuse correlation spectroscopy

Jameson P. O'Reilly^{a,b}, Noah J. Kolodziejski^b, Daniel McAdams^b, Daniel E. Fernandez^b, Christopher J. Stapels^b, and James F. Christian^b

^aNortheastern University, 360 Huntington Avenue, Boston, MA, USA 02115-5005

^bRadiation Monitoring Devices, Inc., 44 Hunt Street, Watertown, MA, USA 02472-4699

Abstract

Optical tissue phantoms are necessary for instrument benchmarking and providing a consistent baseline for experiments in various fields of tissue spectroscopy, including diffuse correlation spectroscopy (DCS). To provide the most useful comparisons, a phantom would ideally mimic tissue as closely as possible, including the geometry of static and dynamic scatterers. A branching design that keeps the capillary cross section constant ensures that the same flow velocity is found throughout the phantom while allowing for single input and output fittings to feed all of the capillaries simultaneously. The direction of each capillary is randomized every few millimeters by randomly allocating 2 by 2 “twisting” squares within each layer. These squares swap the locations of four adjacent artificial capillaries either clockwise or counterclockwise. Numerical simulations were used to verify the random walk-like behavior of the capillary paths resulting from this pattern. This is a step toward replicating the randomly varying directionality of actual capillaries. This design was verified by taking DCS measurements at different flow rates of Intralipid through the phantom, demonstrating the effect of the flow rate on the characteristic decay time of the autocorrelation.

Keywords

tissue phantom; biomedical imaging; 3D printing; diffuse correlation spectroscopy

1. INTRODUCTION

Biomedical diffuse imaging research, from testing new techniques to developing instruments for clinical use, requires optical tissue phantoms that accurately represent the optical properties of the human flesh to be probed. Much effort has been put into recreating the absorption and scattering coefficients of tissue^{1,2}, but relatively little attention has been paid to the distribution of moving scatterers, such as red blood cells, within this tissue. Especially for techniques such as diffuse correlation spectroscopy (DCS), which measures blood flow via speckle perturbation resulting from repeated momentum transfer during photon-moving scatterer collisions,³ the geometry of moving and non-moving scatterers in the phantom is just as important as optical coefficients for generating a faithful reproduction of tissue.

Many different types of phantoms have been employed, including liquid, gel and solid phantoms⁴. Liquid phantoms are relatively inexpensive and very easily customizable, but require solid “blood vessel” walls (whose refractive indices should be matched to the fluid medium) to segregate flow. Additionally, it is difficult to control the thermal motion of the “non-moving” scatterers located in the interstitial spaces. A solid phantom remains inert and unaltered between experiments, allowing for effective benchmarking of instruments against a standard. A variety of solid and gel phantoms have been developed, although they generally only have a singular, large tube carrying liquid through the phantom^{5,6}. This is not an accurate model of human tissue, where the majority of movement is blood flowing through capillaries. Improved resolutions available from 3D printing offers a way to introduce the complexity found in real tissue to phantoms without excessive expense.

We designed and fabricated an optical tissue phantom with a flow geometry similar to that of human capillaries. More specifically, the tube walls are optically identical to the interstitial space, each flow channel is smaller, there are many of them, and they have random, non-uniform lateral movement instead of just going straight through the phantom. Since the design can be 3D printed, it is durable and inexpensive. This paper presents the design in detail and also demonstrates that it works as a model for blood flow velocimetry with DCS in human tissue.

2. DESIGN AND FABRICATION

The phantom design consists of two major components. Firstly, in each end cap, the singular opening to be connected to a pumping system successively splits into sets of smaller and smaller tubes, creating many equally-sized passageways with approximately the same total cross section, and thus fluid velocity, throughout the whole phantom. Once the capillaries have reached their final size, they travel with random lateral movement courtesy of a randomized algorithm for switching their placement within a grid. The design was realized and prepared for fabrication in SOLIDWORKS 3D modeling software. The phantom was made in sections and then screwed together so that the support material used for printing could be removed from the capillaries.

2.1 Connection and Branching

The path through the phantom begins with one opening, analogous to an artery, to simplify connecting it to an external system. The face of the artery has an area that is 5% of the total cross sectional area of the phantom, and this ratio is maintained throughout the phantom to ensure a uniform pressure and fluid velocity profile. To further facilitate easy connection, on top of this opening, there is another layer with NPT standard threading to connect to a nominal 1/16th inch pipe or tube connector.

The multiple capillaries are created by repeatedly branching the initial artery rather than requiring a relatively complicated system of parallel and branching tubing between the pump and the many capillaries of the phantom. At the first junction, the main artery is intersected by four equally-sized tubes that move away from each other perpendicularly in the lateral plane. The total cross sectional area of the four diverging tubes is equal to the area of the original artery, meaning that the radius of each is half the radius of the artery. Each one takes

up a quadrant of the phantom and the dividing process is repeated until the desired capillary size is achieved. In human beings, true capillaries tend to have diameters on the scale of tens of microns. However, due to fabrication constraints to be discussed in more depth later, the smallest capillaries successfully tested were fabricated with a nominal 1.6 millimeter diameter, whose effective diameter were reduced due to the limited resolution of hidden negative space in 3D printing and the surface chemistry/wettability of the material. Regardless, the method described here can, in principle, be applied to any scale as additive manufacturing technology improves.

2.2 Lateral Random Movement

The branching design results in the capillaries being evenly spaced apart in a grid. Each body piece of the phantom was made in layers, and the grid was preserved on both faces of each layer to assure continuity when the layers are put together.

Within each layer, the default for each tube was to travel straight through. Random lateral movement was introduced by randomly placing “switch blocks,” as in Figure 2, within the layers with a fill rate of 62.5%. Wherever a “switch block” was not placed, the capillary just continued straight through the layer.

These blocks switch the positions of four capillaries, which maintains the grid face and ensures that each capillary can be matched up with something in the next layer and thus keep flowing through. They were randomly positioned within the layers and switch in either the clockwise or counter-clockwise direction, also chosen randomly. All “random” decisions were made using a Python-based random number generator.

For testing, one section was made without the lateral movement and one with it. The twisting section had four layers of the 16 by 16 grid. Each capillary made an average of 2.5 lateral switches because not every space was filled with a twisting block. The expected lateral displacement for a two dimensional random walk of this length is the square root of the length, so 1.58 blocks. The true average displacement from where each tube began in the grid was 1.36 blocks. This was determined by tracking the movement of each capillary as the layers were randomly generated and averaging the total distance between each one's starting and ending positions.

2.3 3D Printing and Fabrication

The phantom used for testing was printed in five parts on a Formlabs Form 1+ stereolithography printer. Two end caps, two body sections with twisting capillaries, and one section with capillaries straight through were printed with Formlabs White Standard Resin and a layer height of 50 microns. The capillaries in the test phantom had a minimum diameter of ~1.6 millimeters because previous prints with smaller sizes had blockages caused by leftover support material and printing errors.

Earlier versions of the phantom, with smaller final capillary sizes, were subjected to ultrasonic baths of various solvents, including ethanol, hydrogen peroxide, and heavy-duty cleaners in an effort to remove support material from the capillaries. Water pressure was also ineffective. The small size and movement of the capillaries made it difficult to scrape the

material out as well. Additionally, a printing defect anywhere in the capillary could block it and render it useless. The capillary diameters were increased until all were able to be cleared, which led to a minimum size of ~1.6 mm.

3. VERIFICATION METHODS

The five sections of the phantom were bolted together and plastic tubing was attached to each side with NPT connections. One end of the tubing was connected to a simple syringe pump and the other was placed within a reservoir of either 10% emulsion Intralipid or water, depending on the run. Bubbles were removed from the system by infusing it with the pump until liquid came out the other side and then withdrawing with the tubing inside the reservoir until the syringe was full. A patch containing fiber optics for both illumination and detection was clamped on top of the phantom. The illumination and detection fibers were separated by 5 millimeters.

Autocorrelation plots were taken using a multi-channel diffuse correlation spectroscopy (DCS) instrument⁷ developed at RMD, Inc. for both the twisting and straight sections of the phantom. Three 30 second runs were completed for each section with the syringe pump pushing Intralipid through the phantom at 0, 0.2, 10, and 20 ml/min, as well as water at 20 ml/min and Intralipid pushed through by hand at about 30 ml/min. Nonlinear curve fitting was carried out in OriginLab to find the characteristic decay time of the autocorrelation curves.

The hand-pushed trials were conducted to rule out the possibility of transmitted vibrations from the syringe pump causing the decay in the autocorrelation signals. The flow rate for these trials was estimated to be 30 millimeters per minute based on the length of the trial and the amount of liquid pushed through during this time.

Other sources of error included tiny bubbles remaining in the Intralipid and the collection and/or illumination fibers coming off of the phantom. The fibers must be held flat on the surface they are probing to work properly, and the hardness of the phantom means that any slight deviation will cause the fiber to lose contact with the surface.

4. RESULTS AND DISCUSSION

For both the twisting and straight tube sections, the characteristic decay time of the autocorrelation decreased with an increase in the flow speed of the Intralipid. This can be seen quantitatively in Table 1 as well as qualitatively in Figure 3. The data was normalized to have identical maximum and minimum values. The y-intercepts and limit values of the graphs have complicated and not fully-understood relationships with noise and make it difficult to compare decay time values by eye without normalization.

Pumping water through the phantom led to a flat autocorrelation graph, suggesting that the decay in the other autocorrelations was indeed caused by the moving scatterers in the Intralipid. This was further confirmed by the fact that the decay was still present when Intralipid was pumped through by hand, which also rules out the possibility of vibrations from the syringe pump causing the decay.

This relationship between flow speed and a characteristic of the autocorrelation is all that is needed for DCS at its most basic level^{3,5}. The phantom exhibits the pattern that it needs to replicate in order to be useful for baselining *in vivo* DCS experiments and instrument testing. This happens both with and without the random lateral movement introduced to the capillaries by the random placement algorithm. In fact, there is no noticeable, consistent difference between the two. Notably, it also happens in previous, basic phantoms with a single, large tube running through them^{6,7}. This suggests that unlike Doppler-based techniques, DCS is insensitive to the direction of the flow that it is measuring.

Since the idea of designing a phantom is to create the “golden standard” that *in vivo* experimental data can be compared to, there is no clear way to compare the results from different phantoms and declare one to be more accurate than the others. It is comparable to evaluating different answer keys for the same test. Rather, a good general principle is to make the model as similar to what is really being tested as possible. In this case, DCS is used to monitor the blood flow velocity through human capillaries, so the small, numerous, and non-straight tubes of this phantom design better mimic the real thing than previous phantoms.

5. CONCLUSIONS AND FUTURE WORK

The geometry of flow in this phantom design is a significant step forward from the current field standards. Although it is here only shown to work with DCS, it is similar enough to other, previous phantom designs that it should work with other techniques. Furthermore, improving the flow geometry in any phantom makes it better. While the optical coefficients and mimicking the heterogeneity of tissue are also important, this design does not exclude the use of other work to that end.

In addition to future resolution improvements allowing for smaller capillaries, the customizability of 3D printers offers many opportunities for combining this work with efforts to recreate the scattering and absorption coefficients and multilayer structure of tissue in a phantom^{8,9}. This, in turn, leads to phantoms that better represent what they are supposed to model and ultimately more accurate benchmarking and more consistent testing.

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Figure 1.
Design of endcaps including NPT connection, branching, and wings for screwing together with other phantom components. All measurements are given in millimeters.

Figure 2.

a) A single “twisting” block. b) One of the body pieces of the phantom, composed of randomly placed “twisting” blocks and straight pieces of pipe to fill in the gaps. Again, all measurements are presented in millimeters.

Figure 3.

DCS autocorrelations curves from the validation experiments. Results for both the straight and twisting capillary sections of the phantom are presented, including syringe pump runs of different speeds and the hand-pumped run for each. Every curve comes from averaging the three curves produced by three different 30 second runs.

Figure 4.
DCS autocorrelation curve of distilled water being pumped through the phantom with a syringe pump.

Figure 5. Characteristic decay times, found through numerical analysis of DCS autocorrelation curves in Origin, versus the flow speed through the phantom when the data they are derived from was taken. Demonstrates inverse relationship between flow speed and characteristic decay time of the autocorrelation curve.

Table 1

Characteristic decay time τ of each DCS autocorrelation curve.

Flow Speed (ml/min) and Pump Method	Straight Section Decay Constant (μs)	Twisting Section Decay Constant (μs)
0 (Syringe)	180.609 ± 8.619	224.446 ± 9.902
0.2 (Syringe)	179.770 ± 7.769	197.745 ± 8.782
2 (Syringe)	101.261 ± 6.244	117.738 ± 7.404
10 (Syringe)	91.3012 ± 6.0550	54.1494 ± 4.9506
20 (Syringe)	69.2936 ± 5.9641	62.7901 ± 5.8693
~30 (Hand)	32.3643 ± 3.1082	65.4981 ± 5.6902