Depth Discrimination in Acousto-Optic Cerebral Blood Flow Measurement Simulation
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ABSTRACT

Monitoring cerebral blood flow (CBF) is crucial, as inadequate perfusion, even for relatively short periods of time, may lead to brain damage or even death. Thus, significant research efforts are directed at developing reliable monitoring tools that will enable continuous, bedside, simple and cost-effective monitoring of CBF. All existing non-invasive bedside monitoring methods, which are mostly NIRS based, such as laser Doppler or Diffuse Correlation Spectroscopy (DCS), tend to underestimate CBF in adults, due to the contamination of extra-cerebral tissues to the obtained signal. The contribution of extra-cerebral tissues must be eliminated and data from the depth (brain) should be extracted and discriminated. Recently, a novel technique, based on ultrasound modulation of light was developed for non-invasive, continuous CBF monitoring (termed ultrasound-tagged light (UTL or UT-NIRS)), and shown to correlate with readings of 133Xe SPECT and laser Doppler. We present a comprehensive computerized simulation, modeling this acousto-optic technique in a highly scattering media. Using the combination of light and ultrasound, we show how depth information may be extracted, thus distinguishing between flow patterns at different depths. Our algorithm, based on the analysis of light modulated by ultrasound, is presented and examined in a computerized simulation. Distinct depth discrimination ability is presented, demonstrating that by using such method one can effectively nullify the contribution of extra-cerebral tissues to the obtained signals, and specifically extract cerebral flow data.

Keywords: Blood Flow, Acousto-Optic, Simulation, Depth discrimination

1. INTRODUCTION

Monitoring cerebral blood flow (CBF) is crucial, since inadequate perfusion might lead, in a matter of minutes, to brain damage or even death. It is critical for managing patients who are unconscious or anesthetized, as it provides an indication whether the brain is receiving an adequate supply of nutrients (such as oxygen or glucose). Thus, significant research efforts are directed at developing reliable monitoring tools that will enable continuous, simple and cost-effective monitoring of CBF\textsuperscript{1}.

Optical methods, which provide non-invasive blood flow related measurement, are particularly attractive since they are simple to use, inexpensive and do not require ionizing radiation of radioactive agents. However, most of these methods suffer from a crucial inherent disadvantage emanating from the nature of light diffusion through tissue. As light travels through both cerebral and extra-cerebral tissues, the measurements obtained using most optical methods are not specific to brain tissue. In fact, due to the rapid decay of light when diffusing through highly scattering media, only a small portion of the backscattered light actually interacts with deeper layers, while most of it will be affected by shallower, irrelevant tissue layers. Computer modeling of NIR light propagation has shown that in adult head, approximately 20% to 30% of the typical volume of tissue examined by conventional Near Infrared Spectroscopy (NIRS) equipment is actually brain, while 70% to 80% is extra-cerebral, i.e., scalp and skull\textsuperscript{2}. Thus, even though the blood flow in the scalp and skull regions might be expected to be only about 10-15% in magnitude of that in the cortex\textsuperscript{3}, its contribution to the optical signals can be significant and can lead to incorrect interpretation of physiological responses in deeper brain tissue\textsuperscript{3}. Hence, there is an evident need to reduce the contamination of the brain related signal by extra-cerebral regions and provide a signal that is correlated primarily to brain tissue perfusion.

Recently, a novel non-invasive method for measurement of deep tissue blood flow based on coherent NIR light scattering and the acousto-optic effect, named Ultrasound Tagged Light (UTL)\textsuperscript{5, 6}, was presented and shown to correlate with readings of 133Xe SPECT\textsuperscript{7} and laser Doppler\textsuperscript{8}. This is a hybrid technique which combines ultrasonic resolution with optical contrast, thus enabling better spatial resolution of the tissue optical properties. A computerized simulation modeling this method was previously introduced\textsuperscript{7} and shown to accurately describe related physical phenomena. Herein

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we widen the observation and further validate that this approach is depth sensitive, thus able to distinguish blood flow patterns at different depths. Using such a method, one could reduce the contamination contributed by superficial flow, through extra-cerebral tissues, and enable a direct, non-invasive measurement of cerebral perfusion in a desired predetermined specific depth, while benefitting from all the advantages of light based technologies.

2. METHODS

2.1 Basic Acousto-Optic Simulation

Our acousto-optic method was implemented in a computerized Monte-Carlo simulation using Matlab® environment. The exact specifics are detailed elsewhere. In summary, light emanating from a coherent point source is transmitted towards a highly scattering medium (tissue). The back reflected light is collected by a detector located at a predetermined distance from the source. The tissue is defined by its optical properties (scattering coefficient, absorption coefficient and anisotropy factor) which govern the photons' diffusion through it. A Monte-Carlo approach was utilized to produce photon trajectories within the tissue, which were subjected to scatterer motion caused by blood flow or Ultrasound (US) field (see Figure 1). While the simulation can also accommodate Brownian motion, for simplicity reasons, it was neglected herein and only flow patterns and US fields were considered as the sources of motion of scatterers within the tissue. The simulated motion produced a change in scatterers' positions within the same trajectories (i.e. the identity of these trajectories was kept during their deformation). Each motion type was defined by a characterizing scatterer displacement expression that was applied to specific scatterers, thus changing the overall photon optical paths and causing a corresponding phase shift. The total phase increment of each trajectory was calculated as the sum of all individual phase shifts of moving scatterers in each trajectory using the following equation:

\[ \Delta \phi_i = \sum_{i=1}^{N} \vec{Q}_i \cdot \Delta \vec{r}_i \]  

where \( \vec{Q}_i \) represents the wave vector (\( k_i \)) difference between consecutive scattering events (\( i \) and \( i+1 \)) of the optical path (\( \vec{Q}_i = \vec{k}_{i+1} - \vec{k}_i \)), see Figure 1 - right), and \( \Delta \vec{r}_i \) represents the displacement of the \( i^{th} \) scatterer due to the motion within the tissue. \( N \) is the number of scatterers in trajectory \( \alpha \).

\[ \Delta \phi_i = \vec{Q}_i \cdot \Delta \vec{r}_i \]

Figure 1: An illustration of one photon trajectory obtained from the transmission to the reception point. Black spheres represent scatterers along the trajectory. The \( i^{th} \) scatterer is shifted by both flow and US field. This phase shift is summed up with phase shifts of other scatterers in this trajectory to obtain the overall phase increment along the path. On the right – an illustration of \( \vec{Q}_i \).

Then, for each time step, the overall field at the detector was determined, using Eq. (2)

\[ A_{\alpha} = W_{\alpha} e^{-ih_\alpha} \]  

where \( W_{\alpha} \) denotes the weight or "absorption" behavior of the path (taken into account in the MC simulation). The corresponding intensity signal was then obtained, according to the following Eq. (3)
Blood flow was modeled as directional flow (parallel to the transmission plane) with constant velocity amplitude $V$. The displacement expression over time for the $i^{th}$ scatterer is given by:

$$\Delta \vec{r}_{i, \text{flow}} = Vt \cdot \hat{y}$$

where $\hat{y}$ is a unit vector in the flow direction, $V$ is the velocity and $t$ is time.

The US field was modeled as a continuous and sinusoidal field (with a confined spatial width). Its effect on scatterers is modeled by a periodical motion along the transmission axis $(z)$ at the US central frequency. The displacement is therefore described by the following expression:

$$\Delta \vec{r}_{i, \text{US}} = U_0 \sin \left( \omega t + \varphi_i \right) \cdot \hat{z}$$

where $U_0$ is maximal amplitude of the scatterer displacement due to the applied US field, $\omega = 2\pi f$ is the US angular frequency, and $\varphi_i$ is the US phase for the $i^{th}$ scatterer. The US field exhibits a different phase for each scatterer due to its different position along the $z$ axis (modulated by the US wave at a different delay). $\hat{z}$ is a unit vector in the $z$ direction to represent a displacement along the US propagation axis.

### 2.2 Depth Discrimination Algorithm

Backscattered light emanating from a coherent light source and propagating through a highly scattering medium result in an interference pattern on the surface of the detection plane, usually referred to as a 'speckle pattern'. It is a well established fact that in case the scatterers in the sample undergo movement (e.g. flow), the obtained light speckle pattern fluctuates, and its de-correlation time is proportional to the inverse of the average velocity\(^{11-13}\). This fact was previously demonstrated using our Monte-Carlo simulation\(^9\), demonstrating different decay rates for intensity autocorrelation functions obtained in the presence of different flow velocities. However, the aforementioned simulation was implemented on a homogenous tissue with uniform properties for the whole medium, meaning that flow with a certain velocity, was applied to the whole tissue with no segmentation or separation into layers of flow regions versus static regions and no reference to depth information. As the intent of this study is to discriminate between flow patterns at different depths, we implemented a flow pattern in one layer (1 mm width – see Figure 2 (left)). Then, we changed the depth of this layer and checked how the flow layer's depth affects the results.

Similarly, in the previously described simulation, when US modulation was applied to the tissue, it was uniformly applied to the whole medium, essentially modeling a continuous wave (CW) US introduced to the tissue. In order to enable depth discrimination and locate the layer from which flow is measured, an US pulse propagating through the tissue had to be implemented. Thus, we chose a certain layer thickness (4 mm), which was tagged by US, and incrementally shifted this layer deeper and deeper (0.2mm increments), as the US pulse is propagating deeper (see Figure 1 (right)). Each US location within the tissue corresponds to a different time delay from the pulse transmission. The depth of the flow layer was kept constant throughout the US propagation.

![Figure 2: The simulation setup. The pink square represents the tissue, characterized by its optical properties. Black spheres denote scatterers, moved by the characterizing displacement (due to flow or US). On the left (A), one can observe the different layers. In the blue layer photons encounter moving scatterers due to flow, and its depth is kept constant through the specific simulation (it is changed between different simulations). In the yellow layer photons are tagged by the US. In order to create the full picture of pulse propagation, this layer is shifted in 0.2mm increments to scan the whole tissue. The right side (B) represents the US layer locations in two consecutive steps (yellow – step 1, red – step 2), and the shift is apparent.](http://proceedings.spiedigitallibrary.org/)

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To generate a depth dependent flow measurement, rather than observing the intensity autocorrelation function as we did in the aforementioned simulation, we used spectral analysis and examined the power spectrum of the detected light intensity.

When light propagates through the US modulated tissue volume, its phase is "tagged" (modulated), and the speckle intensity of the scattered light is modulated in correlation with the ultrasound signal frequency. When further scattered by moving blood cells, the tagged light undergoes slight Doppler shifts relative to the original acoustic signal. Hence, the spectral distribution of the US tagged light around the US frequency exhibits an additional spectral broadening, which is proportional to the averaged velocity. Due to the nature of light propagation within the tissue, the obtained spectrum width is an accumulative parameter which is influenced by the entire photon path. At each scattering site along this path, the optical wave acquires a certain phase shift due to movement of scatterers. The overall spectral width is a result of many such phase shifts along the optical path and lacks range discrimination. However, using an US pulse propagating through the tissue, each US location (which corresponds to a certain time delay from its transmission) can be associated with a corresponding power spectrum. Subtraction of spectral widths of adjacent power spectra obtained from consecutive tissue layers provides the net broadening caused by the desired layer, and reduces the influence of shallower ones. The differential spectral width, termed "local broadening", is in fact a depth dependent flow index (FI). The time delay at which changes in the spectral width occur are attributed to location (depth), while the broadening magnitude – to volumetric flow rate.

Practically, for each US location, the intensity temporal pattern on the detector’s area was obtained (as aforementioned by Eq. (3)), and the corresponding power spectrum (PS) was calculated, using

\[ PS = |FFT(I)|^2 \]  

(6)

Prior to FFT (Fast Fourier Transform) calculation, the signal was smoothed by Blackman window to reduce ringing effects originating from the software's zero padding while calculating the FFT. Stacking the obtained power spectra (corresponding to different US layer depths) one next to the other yielded a 2D spectrogram.

To estimate the spectral width, two parameters were calculated for each US depth, the area under the spectrum curve (AUC) in a predetermined bandwidth (BW) around the central US frequency, and the PS amplitude at the central US carrier frequency (A(fUS)). The spectral width (SW) was then calculated by

\[ SW = \frac{AUC}{A(f_{US})} \]  

(7)

Local broadening, which is the Flow Index (FI) as explained before, was determined by the first derivative of the spectral width according to the depth (Eq. (8)).

\[ FI = \frac{\partial(SW)}{\partial Z} \]  

(8)

### 3. RESULTS

The simulation’s ability to measure flow and discriminate flow patterns at different depths was investigated. Spectral analysis (in the temporal frequency domain) of backscattered light intensity signals was applied and examined. The simulation’s output comprises three curves, as illustrated in Figure 3 for the case of a flow pattern through a specific layer. In this case, the flow layer was located between 13-14mm from the surface, velocity was set to 5mm/sec and US pulse width was 4mm with incremental displacements of 0.2mm. The upper panel, Figure 3(A), exemplifies a normalized color coded spectrogram, which is a visual representation of the light spectrum around the US carrier frequency (1MHz) as it varies over depth. The middle panel, Figure 3(B), shows the corresponding calculated spectral...
width as a function of depth. It is clearly seen that narrow Spectral Widths (SW) are obtained from shallow depths and a significant broadening occurs as the US pulse propagates through the flow layer. The SW remains constants as the US passes the flow layer. The "local broadening" as previously defined as the Flow Index (FI), is plotted in the lower panel, Figure 3(C). As expected, the local broadening exhibits an increase around the flow layer, followed by a decrease.

Figure 3: An example of the simulation's output. Upper panel (A) demonstrates a normalized color coded spectrogram. X axis corresponds to depth, Y axis represents the frequency, and color stands for amplitude in arbitrary units. Spectra obtained at different depths are plotted one next to another, thus creating the 2D image. The middle panel (B) contains the matching spectral width, and the lower one (C), the obtained local broadening (FI).

To further validate the simulation's ability to differentiate between different flow velocities, the simulation was repeated with four flow velocity magnitudes (1mm/sec, 2mm/sec, 3mm/sec and 5mm/sec) while keeping the flow layer depth constant (9-10mm). Results are presented in Figure 4, exemplifying distinct differentiation between the three cases and providing decisive evidence to the method's ability to measure different flow magnitudes.

Figure 4: Simulation’s results for 4 different flow velocity magnitudes. Spectrograms (A), spectral width (B) and “local broadening” (C) curves exhibit evident differentiation between disparate velocity magnitudes.
Observing the obtained spectrograms (A), one can easily recognize an increase in spectral width adjacent to the flow layer. The spectral broadening is larger as the flow velocity increases. This effect is further manifested in the spectral width curves (B), in which we can evidently see a different final spectral width for each flow velocity. The spectral width rises adjacent to the flow layer, however remains constant for all deeper layers because of the cumulate nature of the spectral width, as discussed before. In contrast, the spectral local broadening, which is the first derivative of the spectral width, demonstrates a rather narrow peak centered at the flow layer, with different peak amplitudes corresponding to different flow velocity magnitudes. This relationship between the FI peak to the flow velocity magnitude is better illustrated in Figure 5, presenting a linear connection between the two variables ($r^2=0.995$).

![FI Peak Vs. Flow Velocity](image)

**Figure 5:** Local broadening peak values, obtained around the flow layer, for different flow velocity magnitudes. A linear connection is apparent, with $R^2=0.995$.

As the main focus of this study was to demonstrate the method’s depth discrimination ability, the simulation was performed for 3 different flow layer depths (9-10mm, 13-14mm, 15-16mm) while keeping the flow velocity constant. Results are illustrated in Figure 6.

![Simulation’s results for 3 different depths of the 1mm wide flow layer.](image)

**Figure 6:** Simulation’s results for 3 different depths of the 1mm wide flow layer. Spectrograms (A), spectral width (B) and spectral broadening (C) curves exhibit apparent depth discrimination ability.
Depth discrimination is clearly apparent, as the spectral broadening occurred at different depths, as expected. We further utilized the simulation to model a supplementary case in which two flow layers, shallow and deep, are generated in simultaneously.

Figure 7 (A) shows the normalized spectrogram obtained by the simulation in this state. Dashed black lines represent the two flow layers at 9-10mm and 17-18mm. The flow velocities were chosen to be 2mm/sec and 5mm/sec, respectively, though a similar effect was observed when identical velocities were chosen for the different depths as well. Flow index (which is the local broadening parameter) results are also presented in Figure 7 (B). Red curve depict the case of flow pattern only in a shallow layer, whereas the blue one shows two simultaneous flow patterns. The curves are normalized to the maximal amplitude of each curve, and therefore their amplitudes cannot be compared.

One may note a clear identification and localization of both flow layers, suggesting that discrimination and elimination of shallower (superficial) flow effect is indeed feasible and achievable.

4. DISCUSSION

NIRS based methods can provide a continuous, non-invasive tool for measuring cerebral blood flow. However, these techniques are usually affected and contaminated by signals originating from extra-cerebral tissues, through which light diffuses before and after propagating through the brain. Here we presented an acousto-optic based technique which is able to extract flow patterns from a specific depth within a sample. Depth discrimination, as well as identification of two parallel flow patterns located at different depths, shallow and deep, separated by 8mm, were demonstrated in computerized simulations. These results imply that using such a method one can effectively reduce contamination of blood flow measurement by extra-cerebral layers, and specifically extract cerebral flow data.
Figure 4 exemplifies the simulation’s results for different flow velocity magnitudes. The presented results demonstrate the ability to measure flow changes within a tissue. However, FI is presented here in arbitrary units and lacks calibration to absolute values. Previous works, aimed for laser Doppler application, have already shown that blood flow parameters, such as velocity magnitude and the concentration of moving blood cells, can be determined from light intensity spectrum fluctuations. In the future, the simulation detailed here can be utilized as a guiding tool in the quantification process of non-invasive measurement of blood flow based on the acousto-optic effect.

Though it was previously proven that this simulation is able to accurately model Brownian motion as well, its effect was neglected herein. The addition of Brownian motion may affect tissue de-correlation times and add additional phase shifts which may alter the obtained intensity and its power spectra. Since the magnitude of scatterers motion caused by flow is prone to be much bigger than the one caused by Brownian motion, one can expect that the effect of Brownian motion will be minor and not impair the results described here. This issue should be further examined in future work.

While the proposed algorithm was validated in simulation, it should be further investigated in in-vitro and in-vivo experiments and eventually in clinical trials as well. In an actual application, rather than using US pulses as depicted here, the use of continuous pseudo random coded US waves or a coded wave with a narrow autocorrelation function (such as a Golay code) should be considered to increase signal to noise ratio. These may enable satisfactory temporal and spatial resolution to generate a real time continuous blood flow measurement.

Finally, a novel algorithm combining ultrasonic resolution with optical contrast, thus allowing identification of flow patterns as a function of depth within a sample, was introduced and validated. The inherent advantages of being continuous, non-invasive, and easy to use make this US Tagged NIRS (UT-NIRS) technique very promising. The depth discrimination ability presented here is a powerful added value distinguishing this technique from other available NIRS devices.

REFERENCES


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**Introduction**
- Monitoring cerebral blood flow (CBF) is crucial, as inadequate perfusion, may lead to brain damage or even death.
- All existing non-invasive bedside monitoring methods, which are mostly NIRS based, tend to underestimate CBF, due to the contamination of extra-cerebral tissues.
- We developed a novel non-invasive method for CBF monitoring based on light scattering and the acousto-optic effect, termed Ultrasound Tagged Light (UTL).
- We show in computerized simulation, how depth information may be extracted, thus distinguishing between flow patterns at different depths.

**Main Principle:**
- Power Spectrum of US modulated light broadens in the presence of flow, due to Doppler shifts.
- The spectrum width is an accumulative parameter influenced by the entire photon path.
- Subtraction of consecutive spectral widths provides the net broadening caused by the desired layer.

**Methods**

**Simulation's Workflow:**
- A single simulation run yields the modulated light PS
  \[ \alpha \rightarrow \phi_{\alpha} \rightarrow I = \left| \sum_{n=0}^{\infty} e^{-|\phi_{\alpha}|} \right| \rightarrow PS = |FFT(I)| \]

- Photon Trajectories (Monte-Carlo) ➔ Phase Increment for each Trajectory ➔ Amplitude & Intensity calculation ➔ Power Spectrum

- Flow and US are confined to certain layer within the tissue
- Consecutive runs simulating a propagating US pulse
  - Flow layer depth remains constant
  - US layer gets deeper

- Power Spectrum for each US depth is obtained

**Results**

**Flow Velocity Dependency:**
- Flow Index peak amplitude is linear with flow velocity magnitude

**Flow Depth Dependency:**
- Flow Index peaks at different depths corresponding to different flow channel depths

**Shallow Vs. Deep Flow:**
- Two distinct simultaneous flow channels can be identified

**Discussion**
- Distinct depth discrimination ability is presented.
- Results suggest that nullification of extra-cerebral tissues contribution is feasible.
- Further in-vitro and in-vivo studies should be conducted.