Deep learning model for ultrafast quantification of blood flow in diffuse correlation spectroscopy

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INDEX TERMS

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ABSTRACT

Diffuse correlation spectroscopy (DCS) is increasingly used in optical imaging field to assess blood flow in humans due to its non-invasive, real-time characteristics and its ability to provide label-free, bedside monitoring of blood flow changes. Previous DCS studies have utilized a traditional curve fitting of the analytical or Monte Carlo models to extract the blood flow changes, which is computationally demanding and less accurate as the signal to noise decreases. Here, we present a deep learning model that eliminates this bottleneck by solving the inverse problem more than 2300% faster, with equivalent or improved accuracy compared to the nonlinear fitting with an analytical method. The proposed deep learning inverse model will enable real-time and accurate tissue blood flow quantification with the DCS technique.

INTRODUCTION

Blood flow has been investigated as an important biomarker for a variety of diseases in humans. Most diseases induce changes in blood flow thus blood flow parameter can be indicative of the diseases. Blood flow has also been an indicator of muscle activation, where the muscle fibers increase the rate of oxygen consumption and therefore increase the rate of the oxygen supply by increasing blood flow [1], [2]. Several clinical technologies for assessing tissue blood flow are available, including computed tomography and magnetic resonance imaging. However, these modalities provide single snapshot time points, and are not suited for continuous, long-term monitoring at the bedside settings [3]. Laser Doppler flowmetry measures blood flow from a very small volume, while Doppler ultrasound measures blood flow in large vasculatures, and it is hard to use for longitudinal monitoring due to the need for stable ultrasonic probe orientation [3].

Near-infrared diffuse correlation spectroscopy (DCS), also known as diffusing-wave spectroscopy (DWS), is an emerging technique for detecting changes in blood flow in humans. It uses the well-known spectral window in the near-infrared (NIR, 650 to 900 nm) range, wherein the relatively low biological tissue absorption enables deep penetration of light. Since it is label-

free technique, highly suitable for continuous noninvasive measurement of blood flow in biological tissues. In the last decade, DCS technology has been implemented, extensively validated and employed to noninvasively probe the blood flow information in deep tissue vasculatures, such as the muscle and brain functional studies [4]–[9]. Recently we have shown evidence of detecting the functional connectivity between brain regions in humans by inspecting the low-level oscillations in the blood flow changes in the human brain [10], [11].

The current quantification approach of DCS is to iteratively fit measured autocorrelation function decay rate with the analytical or Monte Carlo models. This step can be time-consuming especially for dynamic longitudinal measurements and thus it is performed as postprocessing. However, it is useful to obtain the results on-line as a real-time feedback to the clinicians. Deep learning method allows fast retrieval of parameters, and recently been used in diffuse optical field, including functional near infrared spectroscopy [12]–[14], spatial frequency imaging [15], fluorescence imaging and tomography [16]–[18]. Its application for DCS has yet to be established [19]. Here we detail the deep learning implementation for DCS to quantify blood flow related parameter and with a direct application of assessing the blood flow changes during arm cuff-ischemia protocol on a human subject.

MATERIALS AND METHODS

DIFFUSE CORRELATION SPECTROSCOPY

In this short communication, we are not going into the details of diffuse correlation spectroscopy (DCS) technique, since the details can be found in more recent review [6], [9], [20], [21]. Briefly, the normalized diffuse light intensity temporal autocorrelation function (g_2) is recorded in real measurements. From $g_2(r,\tau)$, the normalized diffuse electric field temporal autocorrelation function, $g_1(r,\tau)$, can be extracted by using the Siegert relation, $g_2(r,\tau) = 1 + \beta|g_1(r,\tau)|^2$. Here β is a constant, y-intercept on the g_2 axis, dependent on the number of spatial modes detected, ranges from 0 to 1. If the coherence length is longer than the photon pathlength, photon detection with a single mode fiber leads to β=0.5 for the unpolarized light. Since g_1 is the normalized version of the electric field autocorrelation function ($G_1(r,\tau)$), which has been shown to satisfy diffuse photon correlation equation based on partial differential equation [22], [23], one can solve this equation analytically or numerically to find $G_{1_model}(r,\tau)$ and g_{1_model}. The dynamic information of the scatterers, moving blood cells in the microvasculature, can be obtained by fitting the model to the experimental data. It has been shown that diffusive motion is sufficiently accurate to model the dynamics in deep tissue with the definition of as blood flow index (BFI), where is proportional to tissue blood volume fraction, is the effective Brownian diffusion coefficient [21]. The g_1 function is traditionally fitted to an analytical or numerical solution of the diffusion equation to estimate the BFI parameter. Experimentally relevant parameter, β, is also fitted. This approach results in a two-parameter fit performed iteratively by using nonlinear fitting algorithm (e.g. lsqnonlin in Matlab) that increases the total computational time. This creates a bottleneck especially when high-speed DCS is used [24] and longitudinal dynamical changes are being investigated with high data acquisition rate. Therefore, there is a need for fast methods to quantify the BFI parameter and the alternative fast implementation with deep learning is detailed in the next section.

For obtaining the experimental data, the typical setup of the DCS technique consists of a laser with along coherence length as the light source, a photon-counting avalanche photodiode (APD)

or photomultiplier tube (PMT) as the detector, and a hardware autocorrelator. As one of the critical components, the autocorrelator computes the autocorrelation function (g_2) of the temporal fluctuation of the light intensity, which was subject to multiple scattering events before emerging from the investigated position on the sample surface. We previously described our DCS system [10], which consists of a continuous-wave laser source (785nm, CrystaLaser, Reno, NV) with a coherence length larger than 10 meters, NIR-optimized single-photon counting modules (SPCM-NIR, Excelitas, Quebec, Canada), and a custom-built eight-channel auto-correlator board (Correlator.com). A multi-mode fiber (1000μm core diameter, FT1000UMT, Thorlabs Inc, Newton, NJ) are used to guide the laser light to the forearm, while a single-mode fiber (5μm core diameter, 780HP, Thorlabs Inc, Newton, NJ) is used to collect the emitted light from the forearm to the SPCM at a known distance (Fig 1). To create blood flow perturbation, a blood pressure cuff was placed on the subject's forearm. Blood flow data were acquired at 3 stages. First, a baseline measurement is obtained, next, the cuff is inflated to 200 mmHg, finally, it is released. Each stage lasts for approximately 45s.

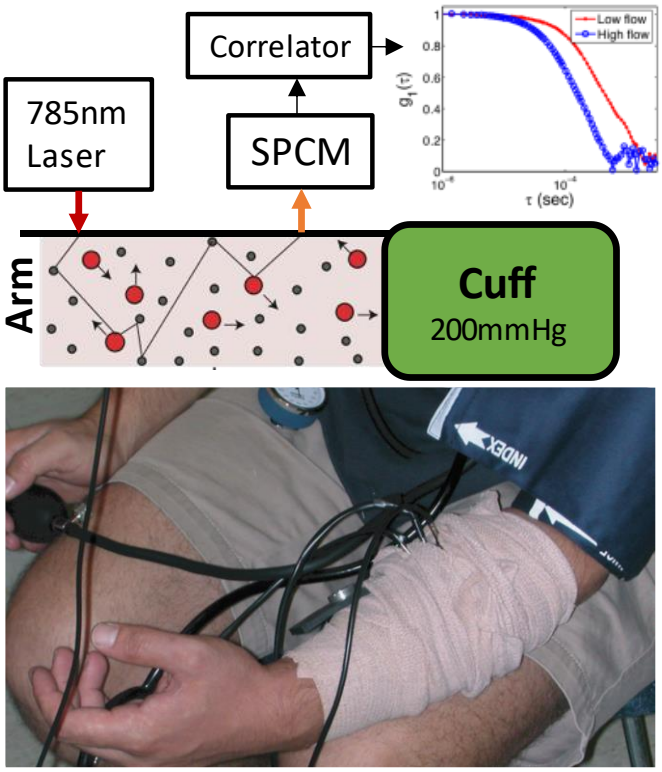

FIGURE 1. The NIR laser is directed onto the forearm via a fiber. Photons injected by laser light scatter from blood cells, which introduce temporal intensity fluctuations at the single photon counting module (SPCM) detector. The SPCM detects the photon and sends a signal to the autocorrelator, which generates the g_2 curve. From g_2 data, one can derive the g_1 curve via Siegert relation (see text for details). Decay rate of g_1 curve is related to blood flow: moving blood cells introduces endogenous flow contrast (sharper decay, higher blood flow). A cuff is also placed on the forearm and pumped to 200mmHg to restrict and perturb the blood flow in the arm muscle microvasculature (low blood flow, slower decay rate-red in color in g_1.

THE DEEP LEARNING NETWORK

We implemented a deep neural network (DNN) to quantify relative blood flow changes, i.e., changes in the blood flow index (BFI, cm^2/s) as a fast approach. The result of the DNN was also compared to the traditional nonlinear fitting approach. We used the structure of MobileNetV2, which is a lightweight convolutional neural network used for the classification of images [25], [26]. We replaced layers on the bottom and top to accept the measured g_2 as input and β and BFI as the output parameters. The power of deep learning lies partially in its ability to automatically detect and approximate nonlinear patterns in high dimensional space [27]. The structure of the DNN is shown in (Fig 2), which uses MobileNetV2 for a total of 161 layers. The model receives an input of 128 g_2 values that are obtained from the autocorrelator at a specific delay time (τ). It is reshaped into a matrix of 32x4 and fed into a 2D CNN (kernel(1,4), stride(1,4)) with 32 filters and transposed in order to map the values into a 32x32 image. The 32x32 image is fed into MobileNetV2 and connected to a fully connected layer of two neurons with a linear activation function that outputs both β and BFI parameters.

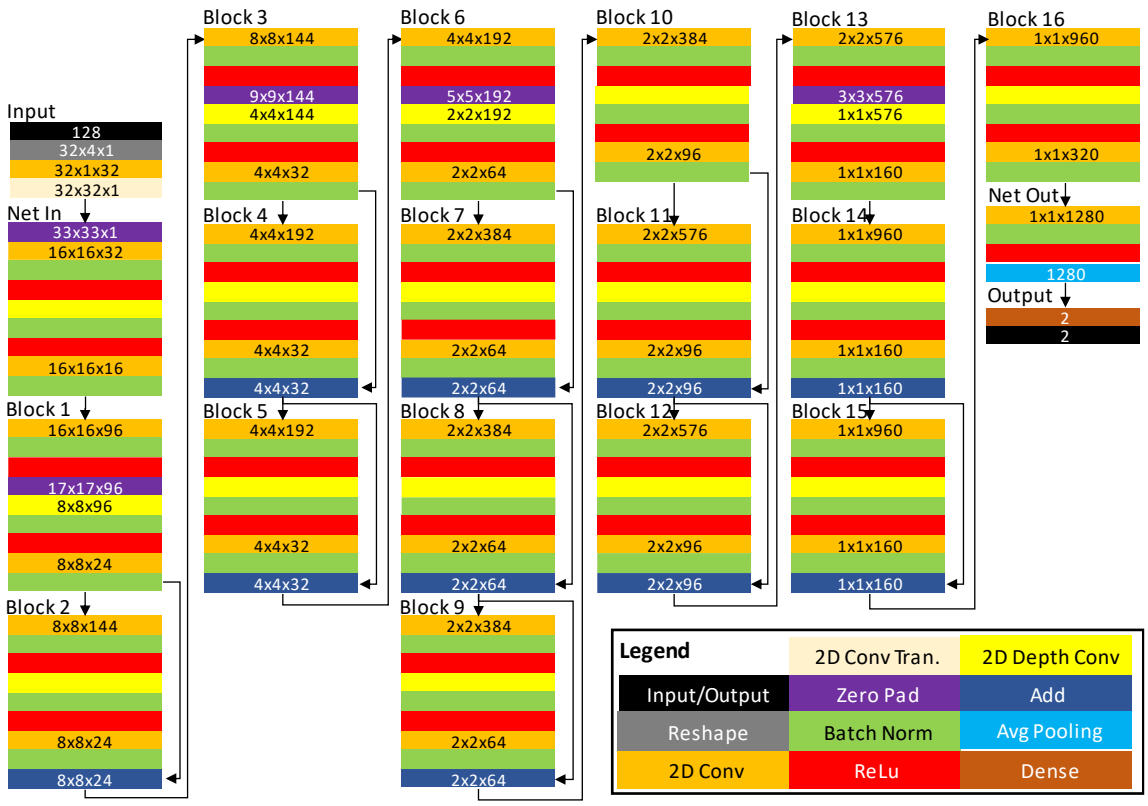

FIGURE 2. The structure of the deep learning network (DNN). It takes in 128 points of the g2 function at a given τ and is reshaped into a 32x4 matrix. Convolutional Neural Network (CNN) is used to map the matrix into a 32x32 image before being passed into MobileNetV2. The output of the MobileNetV2 is connected to a fully connected network of two neurons with a linear activation that gives β and BFI as an output.

The training data were generated by a semi-infinite diffusion model [4], with β sampled from 0.01 to 1 with 120 linearly spaced increments, BFI sampled from 10^{-8} to 10^{-5} mm^2/s with 120

linearly spaced increments, and DCS data noise between 10 to 100kcps with 5 linearly spaced increments for a total of 72000 samples. The samples were split into 70% training, 15% validation, and 15% test sets. The DCS noise was obtained as detailed previously [28] and was added to the data to simulate experimental conditions (Fig 3A, C). The multi-tau scheme of a typical auto-correlator, which increases the number of samples averaged as τ increases (hence the smooth tail) has been considered when adding the noise (Fig 3B). The training of the model was performed using Tensorflow 2.0.0 and the mean squared error (MSE) was minimized as a loss function.

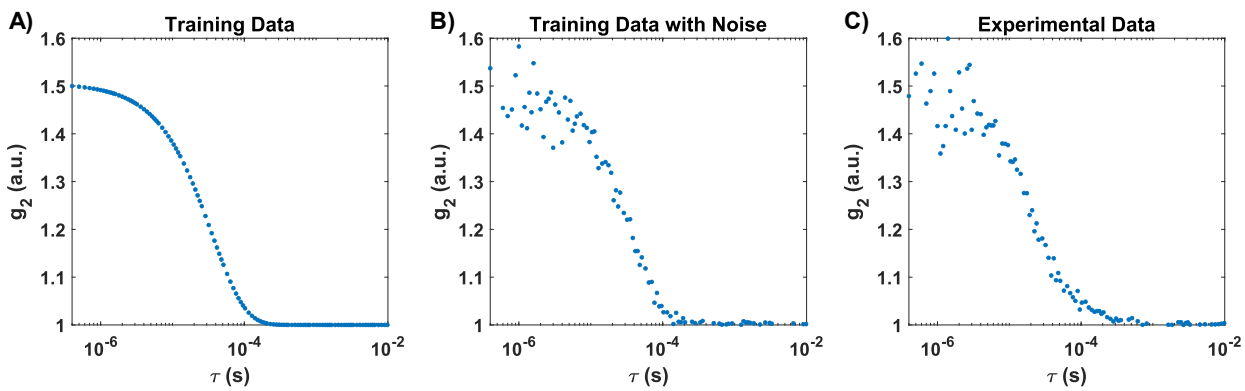

FIGURE 3. (A) The training curve is generated from the analytical solution. This analytical model is typically used to fit experimental data such as in (C). (B) DCS noise between 10 to 100kcps is added to the training data to simulate experimental conditions. The data is fed into the deep network for training so that it can obtain the correct result even under noisy conditions. (C) This is an example of experimental data.

Adadelta was used as the optimizer to adaptively change the learning rate. The training of the model took ~30.5hr to complete 10000 epochs on a graphics processing unit (Nvidia GeForce GTX1080TI). The details of the training progress after 10000 epochs is shown in Figure 4. The model had a validation mean squared error (MSE) of 0.00263 and a training MSE of 0.00067 (Fig. 4A). To check the error against the test set, the predicted value was compared against the target value and the percent error was obtained (Fig 4B). The results show that the predicted β and BFI have 92.3% and 95.6% of all the values within 5% error respectively. The regression of the trained DNN compared to the test data had an R-squared value close to 1, indicating an excellent fit (Fig 4C).

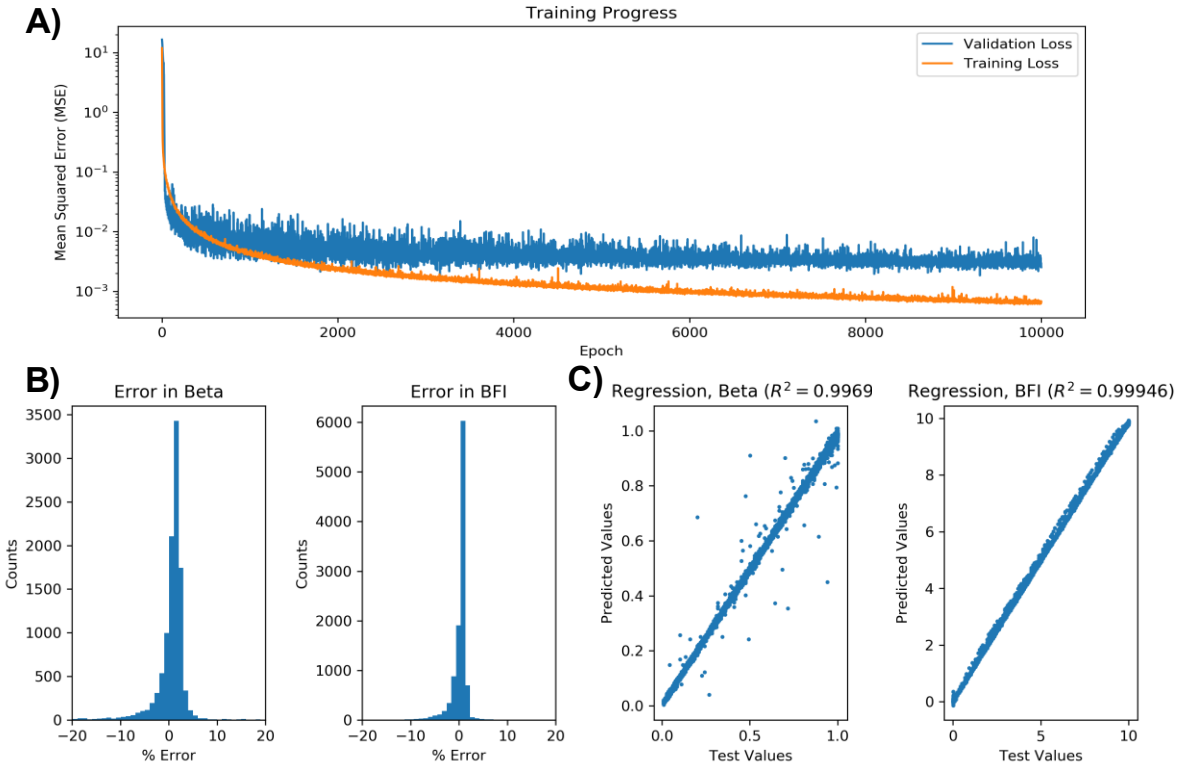

FIGURE 4. (A) Loss function Mean Squared Error (MSE) after 10000 epochs. The final training MSE and validation MSE is at 0.00067 and 0.00263 respectively. (B) The percent error of the predicted test set as compared to the target value in β and blood flow index (BFI). Here 92.3% of predicted β and 95.6% of the predicted BFI falls within 5% error from the target. (C) Linear regression of the predicted test set as compared to the target values for both β and BFI both showed good linearity with an R^2 of close to 1.

RESULT VALIDATION

To validate the model in humans, a pressure cuff experiment was performed to induce occlusion of blood flow in a subject's forearm (Fig 1). The DCS probe was placed on the subject's forearm at a source-detector separation of 2.75 cm with an integration time at 1 s. Data were acquired at a baseline for 45 s, then the cuff is inflated to induce ischemia for another 45 s, and finally, it was released and allowed to return to the resting state for 45 s. The BFI and β were extracted from both the analytical and the DNN models. As Figure 5 indicates clearly, the DNN showed a good correlation with the analytical solution (AS) for both β and BFI parameters. Both models estimated the β values (Fig. 5A) very close to the expected value of 0.5 (AS: 0.488±0.046, DNN: 0.484±0.047). We also measured the computation time taken to generate the 135 data points. The AS fitting method takes 11.19±6.97 ms on each time point to extract BFI and β, while the DNN takes 0.46±0.04 ms on a GPU. This represents a speed increase of more than 2300%.

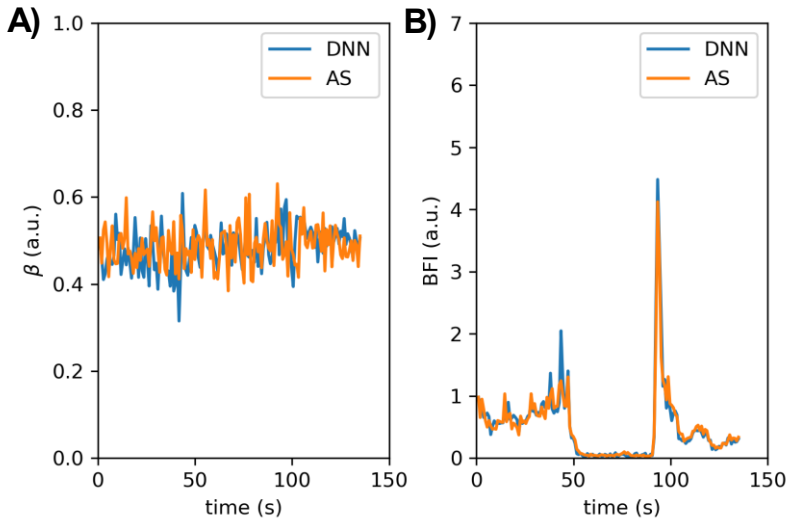

FIGURE 5. A cuff occlusion experiment was performed by placing the cuff on the forearm and pumped to 200 mmHg to restrict the blood flow. The experiment is split into three blocks of 45 s of rest (baseline), occlusion, and rest again. The analytical solution (AS) was compared to the deep learning model (DNN), which both showed a similar trend for quantified β (A) and BFI (B).

SUMMARY

Traditionally, nonlinear curve fitting scheme is used to analyze the DCS data to estimate the blood flow-related parameter (BFI). However, iterative fitting of many data points obtained from dynamic measurements leads to high computation time and cannot provide real-time online processing. Thus, usually in the field post-processing is implemented. In this work, we have shown that deep learning is able to quantify the BFI and β values from the DCS's data with high accuracy. This deep learning approach can also increase the quantification speed by more than 2300%. The accuracy of the model can be improved by further training the model with experimental data on a phantom with known BFIs. Additionally, the optical properties could also be included in the model by adding two additional neurons to the last layer, which could potentially allow for the estimation of the absolute blood flow within the tissue volume. Towards real-time applications, the prediction speed could also be further reduced by pruning weights that are insignificant to reduce the number of calculations needed. This deep learning approach holds the potential to lead to wide-spread use for clinical applications in the DCS field, especially for those require longitudinal, real-time monitoring of dynamic changes such as muscle and brain function studies.

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