Time-domain diffuse correlation spectroscopy: supplementary material

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Monte Carlo Simulations

Transcranial optical methods must balance the sensitivity of the measurement to the brain with the magnitude of the detected signal. Using larger distances between sources and detectors increases the proportion of signal arising from the brain but exponentially reduces signal strength. Similarly, applying a late time-gate increases brain sensitivity but reduces signal levels as photons outside the gate are rejected. Monte Carlo simulations demonstrate that the loss in signal strength from a time-gated diffuse correlation spectroscopy (DCS) measurement can be compensated by reducing the source detector separation, yielding a net improvement in sensitivity to the brain with respect to existing techniques while retaining comparable signal strength (Fig. S1).

A two-layer slab model was simulated to describe the behavior of a transcranial measurement of an adult brain through a realistic layer of scalp and skull. In addition to the usual effects of optical absorption and steady-state scattering, momentum transfer from dynamic scattering simulated the effect of blood flow (BF) on the DCS signal [1]. The geometrical, optical and flow properties of the layers are representative of a single upper extracerebral layer representing scalp and skull and a lower layer representing brain. In particular the thickness of the first layer was set to 10 mm, the optical properties (reduced scattering (μ_s') and absorption (μ_a) coefficients) in the two layers were set to $\mu_s'=12\text{ cm}^{-1}$, $\mu_a=0.10\text{ cm}^{-1}$, and the Brownian Diffusion coefficient (D_B) was set to $D_B=1\text{Ee}^{-6}\text{ mm}^2/\text{s}$ in the top layer and $D_B=6\text{e}^{-6}\text{ mm}^2/\text{s}$ in the bottom layer, as in [1]. Sensitivity to the brain was determined by the fraction of the total signal attributable to the bottom layer. In particular, for TD-NIRS, we simulated the detected intensities for the baseline condition, a 20% increase in μ_a in the bottom layer, and a 20% increase in μ_a in both layers. For TD-DCS, we simulated the detected autocorrelation functions for the baseline condition, a

20% increase in D_B in the bottom layer, and a 20% increase in D_B in both layers. Next we computed the retrieved absorption and D_B by for each case assuming a semi-infinite homogeneous medium. Finally, the relative sensitivity to the bottom layer was computed as the ratio of the retrieved relative change in μ_a or D_B for a bottom layer only change, over the retrieved relative change in μ_a or D_B for a change in both layers. Note that for NIRS, the relative brain sensitivity is simply the ratio of the bottom-layer partial path length over the total path length, as we detail further in [1].

For continuous wave (CW) NIRS measurement of cerebral hemoglobin concentration, source-detector separations are typically 3 cm in adults. Hence we take the detected flux at this distance as a benchmark to which all other fluxes are compared. At this separation, only 23% of the CW-NIRS signal and 38% of the CW-DCS signal arise from the bottom layer. Due to the small aperture detection requirements for DCS, DCS measurements are often made at a shorter separation of 2 cm to increase the detected signal levels. At this shorter separation, the flux increases by a factor of 16, but the CW-DCS sensitivity to the bottom layer drops to 17%. At a 1 cm separation, though the flux increases 500-fold, both CW-NIRS and CW-DCS modalities are essentially insensitive to the bottom layer. Thus, although CW-DCS does have greater sensitivity to the brain than CW-NIRS, in all practical cases a majority of the signal in CW methods still arise from the scalp, not from the brain.

In contrast, time-gating the signals such that only late arriving photons are considered, greatly increases the fraction of the signal arising from the brain. The simulation shows that when the separation is reduced to 1 cm, a time gate starting at 1.5 ns maintains the same flux through the gate as the CW flux with a 3 cm separation. Under these conditions, the TD-NIRS signal from the bottom layer increases to 37% and the TD-DCS signal from the bottom layer increases to 68% with respect to 23% and 38% respectively for the 3 cm CW case.

Fig. S1. TD-DCS Monte Carlo simulations. Panel (d) Slab geometry and optical properties of the two layers. Panel (a) reports the cumulative photon counts arriving after the specific delay time vs. the gate start time. Note that the gate start time indicates the time after which the arriving photon counts are integrated. Photon counts are normalized with respect to the photon counts detected at a 3 cm separation with zero gate start time (i.e. CW). While fewer photons in the TPSF have long times-of-flight, the total number of detected photons increases exponentially with shorter source-detector separations. Panels (b) and (c) report the sensitivity to the bottom layer (brain) as a function of gate start times for NIRS, and DCS, respectively. By using late time-gates, brain sensitivity increases. As the lines across the figures show, by using shorter source-detector separations, we can maintain the same number of photons as CW at 3 cm but gain in brain sensitivity by using late time-gates.

TD-DCS Instrumentation

Initial measurements were performed with a commercial time-correlated single photon counting module (SPC-600, Becker Hickl) prior to the adoption of our custom device. However, any commercial module capable of performing time-resolved fluorescence correlation spectroscopy should be compatible with TD-DCS. The 150 MHz laser clock was divided by eight to bring the TCSPC stop signal rate to within the range of the converter. The stop signal rate is a trade-off between minimizing the effects of non-linearity of the converter and the length of the conversion dead-time, which sets the maximum conversion rate.

Planar structure SPADs, such as those commercially available from MPD, have superior timing resolution, but their thin photon absorption region limits their sensitivity, especially in the near infrared. Reach-through structure SPADs, such as those commercially available from Excelitas, have greater sensitivity but reduced timing resolution. At 852 nm, the detection efficiency of traditional planar structure SPADs is only 10% while the reach-through structure SPADs can achieve 50%. We found the 30% efficiency [2] of red enhanced planar structure SPADs was sufficient for TD-DCS measurements and allowed us to trade some photon sensitivity for better timing resolution. However, commercial reach-through structure SPADs suitable for time-resolved measurements should also be suitable for TD-DCS with

the opposite tradeoff of worse timing resolution for better sensitivity.

The coherence factor β can be doubled by using a polarizer with the tradeoff of reducing the photon flux by more than half. The loss of flux may be compensated by increasing the illumination intensity if the measurement is TSPC converter limited.

After-pulsing from the SPADs can limit the resolution of the measured correlation functions below correlation times of one microsecond. The effects of after-pulsing can be removed by beam-splitting a single mode detector fiber into two detectors and calculating their cross correlation function.

Commercially available single-longitudinal mode lasers can be pulsed for TD-DCS measurements without the amplification stage. The lack of amplification leads to lower source optical powers which can be compensated by using longer integration times and shorter source-detector separations. Optical amplifiers are also available commercially, but the stages must be combined in the lab to build a custom two-stage source. We anticipate new devices, similar to the non-commercial ones used in this work, will enter the market soon, making their improved performance more widely available. Nevertheless, subject to the trade-offs we have enumerated, the TD-DCS technique can be generally performed in labs now using off the shelf components.

Further considerations on β

In CW-DCS the temporal coherence is maximized by choosing lasers with a coherence length longer than the distribution of photon path-lengths through the scattering medium. We maximize the spatial coherence by using a single mode fiber for detection, but as we generally do not use a polarizer, the best value of β we can achieve in conventional CW-DCS is 0.5. For TD-DCS, as we discussed in the results section, the short coherence length of the pulse of light reduces the temporal coherence. Following the formalism of [3], we calculated β for different coherence lengths, different time gate widths and different start times for the time gate along the TPSF to estimate the influence of different pulse parameters on the TD-DCS SNR. For a source-detector separation of 1 cm, index of refraction $n=1.34$, $\mu_a=0.10 \text{ cm}^{-1}$ and $\mu_s'=10 \text{ cm}^{-1}$, as we used for the Monte Carlo simulations above, and measuring all photons, we find that β is reduced to 0.15 when using a 100 ps pulse of light. Longer laser pulses have longer coherence lengths, larger β , and more photons, but reduce the accuracy with which we can path-length resolve the detected light and estimate the scattering coefficient from the TPSF measurements.

Experimentally, in addition to showing the β dependence on the width of the gate used to calculate the correlation function (Figure 3), we also observed a dependence of β on the start time of the narrow gates along the TPSF. In particular, for early gates, before the TPSF peak, β is higher than for gates after the peak (Figure 2s). We believe this behavior is due to the steepness of the TPSF effectively shortening the distribution of photon path-lengths through the gate.

Fig. S2. β as a function of time delay. Measured β for the twelve 48 ps gates shown in Figure 4, during the same experiment.

Additional experiments

To demonstrate the effect of motion on the autocorrelation function, we added motion to a liquid phantom using a magnetic stirrer and we incrementally increased the stirring rate. Figure 3s shows how the TPSF remains constant with increasing stirrer speed, since the TPSF depends only on scattering and absorption, while g_{2s} , which in addition to scattering depends on motion, decays faster with increased stirrer speed.

Fig. S3. TD-DCS signals change with speed. TPSF (panel a) and intensity temporal autocorrelation function (panel b) for a silicone liquid phantom at different stirrer settings. g_{2s} is calculated over a 240 ps gate across the TPSF peak. By changing stirrer speed, the g_{2s} decay rate increases, while the TPSF remains constant since only the speed of the scattering particles within the liquid phantom is changing.

Homogeneous phantom experimental methods

For the experiments presented in Figures 3, 4 and S2, we used whole milk diluted with water (ratio 1:4) to obtain a scattering coefficient of $\mu'_s = 6.2 \text{ cm}^{-1}$ and an absorption coefficient $\mu_a = 0.04 \text{ cm}^{-1}$ (water) at 852 nm, as measured by a combined Frequency-Domain NIRS and CW-DCS device (MetaOx, ISS, Inc. iss.com/biomedical/instruments/metaox). While there is no actual flow in the liquid phantom, the Brownian motion of the scattering particles contributes to the Brownian diffusion coefficient D_B , and for the diluted milk at room temperature with CW-DCS we measured $D_B = 8.5 \times 10^{-9} \text{ cm}^2/\text{s}$. For the experiment of Fig 3s, we used liquid silicone, which is more viscous than milk, to span a larger range of speeds, when stirring the phantom. The optical properties of the silicone were $\mu'_s = 3.5 \text{ cm}^{-1}$, $\mu_a = 0.04 \text{ cm}^{-1}$ at 852nm and $D_B = 1.3 \times 10^{-9} \text{ cm}^2/\text{s}$. All liquid phantoms were contained in a 2000 ml glass beaker and maintained at the room temperature of 24 degrees Celsius. The source and detector fibers were immersed a few mm into the liquid and the source-detector separation was set to 1 cm. Laser power at the distal end of the source fiber was 6.5 mW, with a laser pulse width of 150 ps, and a repetition rate of 150 MHz. For the milk experiments we acquired 276 million photons in 2800 seconds.

Small animal experimental methods

Two female Sprague-Dawley rats were included in this study. Experiments and procedures were approved by the Massachusetts General Hospital Subcommittee on Research Animal Care. During all surgical procedures, the animals were anesthetized with isoflurane (2–2.5%) administered via a facemask in a gas mixture of 80% air and 20% oxygen. After tracheotomy and cannulation of the femoral artery and vein, animals were artificially ventilated and mounted on a stereotactic frame. Heating blankets maintained

core temperature at 36.5–37.5 °C. An optical probe consisting of one source and two detector fibers was secured on the animal head. Isoflurane anesthesia of 1–1.2% was maintained for the rest of the experiment. Continuous monitoring of arterial blood pressure, pulse oximetry arterial oxygen saturation, heart rate with ECG, end-tidal CO_2 , and blood sample recording of arterial pH, PaO_2 , and PaCO_2 at the beginning, middle and end of the experiment, assured maintenance of basic physiological parameters. TD-DCS data were acquired for a baseline normocapnic period of 10 min followed by a 10 min hypercapnic challenge and by a final 10 min normocapnic period. Inspired CO_2 was increased during hypercapnia to 4% and PaCO_2 nominally increased from 35 mmHg to 45 mmHg. While in Figure 5 we report results on only one animal for brevity, results in the two animals were consistent.

References

1. Selb, J., Ogden, T. M., Dubb, J., Fang, Q., and Boas, D. A., "Comparison of a layered slab and an atlas head model for Monte Carlo fitting of time-domain near-infrared spectroscopy data of the adult head," *J Biomed Opt* 19, 16010 (2014).
2. Gulinatti, A., Panzeri, F., Rech, I., Maccagnani, P., Ghioni, M., and Cova, S. D., "Planar silicon SPADs with improved photon detection efficiency," *Quantum Sensing and Nanophotonic Devices VIII* 7945, 79452P–79452P–10 (2011).
3. Bellini, T., Glaser, M., Clark, N., and Degiorgio, V., "Effects of finite laser coherence in quasielastic multiple scattering," *Phys. Rev., A* 44, 5215–5223 (1991).