

An algorithm for assessment of inflow and washout of optical contrast agent to the brain by analysis of time-resolved diffuse reflectance and fluorescence signals*

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Abstract — In optical measurements of the brain oxygenation and perfusion the problem of contamination of the signals with the components related to the extracerebral tissues remains an obstacle limiting clinical applicability of the technique. In this paper we present an algorithm allowing for derivation of signals related to the changes in absorption in the intracerebral tissues based on analysis of time-resolved diffuse reflectance and fluorescence. The proposed method was validated in series of Monte Carlo simulations in which inflow and washout of an optical contrast agent into the two-layered human head model was considered. It was shown that the decomposed intracerebral component of the signal can be derived with uncertainty of about 5%. This result suggests that the method proposed can be applied in improved estimation of brain perfusion parameters based on the bolus-tracking technique.

I. INTRODUCTION

Near infrared spectroscopy (NIRS) is an optical technique which was validated in brain oxygenation assessment [1]. Most advanced NIRS-based method makes use of time-resolved optical measurements [2]. In this method short (typically picosecond) laser pulses are delivered to the studied medium and measurements of distributions of times of flight of diffusely reflected photons (DTOFs) and/or distributions of times of arrival of fluorescence photons (DTAs) are carried out [3, 4]. This method can be used in combination with an injection of an optical contrast agent (typically indocyanine green - ICG) [5-8]. In several studies the technique of monitoring of the dye inflow and washout was validated as a tool for estimation of cerebral hemodynamic parameters [9-12]. Critical problem associated with the use of the NIRS-based techniques is connected with the fact that the measured signals are sensitive to changes in oxygenation and perfusion of intra- and extra-cerebral tissue compartments [13]. In this paper we proposed an algorithm allowing for derivation of signals related to the changes in absorption in intracerebral tissues based on analysis of the time-resolved diffuse reflectance and fluorescence. The algorithm makes use of four input parameters – statistical moments of DTOFs and DTAs which can be measured on the surface of the head during inflow and washout of the optical contrast agent. The proposed method was validated in series of Monte Carlo simulations in

which inflow and washout of an optical contrast agent into the two-layered human head model was considered.

II. METHODOLOGY

A. Monte Carlo simulations

In this study we focused on theoretical simulations based on the Monte Carlo code proposed and described earlier by Liebert et. al [14]. In the Monte Carlo algorithm it was assumed that the scattering properties of the medium at excitation and emission wavelengths are the same, so the excitation and fluorescence photons follow the same paths between source and detector. Weight of every fluorescence photon which is detecting on the detection position was calculated by analysis of probabilities of fluorescence conversion in voxels of the medium and probabilities of survival of excitation photons and emission photons on their paths to the conversion position and from this position to escape point, respectively. The algorithm allows for simulations of the multi layered medium for different combinations of optical properties of the dye and medium at excitation and emission wavelengths. In the present study we analyzed the changes in moments of DTOFs and DTAs for assumed changes in absorption coefficient at excitation wavelength μ_{afx} . Time-dependent changes in μ_{afx} were described by following formula:

$$\mu_{afx}(t) = \frac{C_{ICG}(t)}{C_{ICGmax}} \times (\mu_{afxmax} - \mu_{afxmin}) - \mu_{afxmin} \quad (1)$$

where: $C_{ICG}(t)$ – the modeled concentration of the ICG in tissue as a function of time t ; C_{ICGmax} - maximum value of the modeled ICG concentration for the whole range of t ; μ_{afxmin} and μ_{afxmax} are the parameters allowing to simulate different initial levels of μ_{afx} and amplitudes of the change, respectively [15]. $C_{ICG}(t)$ is described by:

$$C_{ICG}(t) = R(t) \otimes C_{ICGart}(t) \quad (2)$$

where: $C_{ICGart}(t)$ is a function corresponding to arterial input function proposed by Leung et. al. [16] and $R(t)$ is residual function, which can be described by:

$$R(t) = \frac{MTT}{(\beta - MTT)} \left[\exp\left(-\frac{t-1}{\beta}\right) - \exp\left(-\frac{t-1}{MTT}\right) \right] \quad (3)$$

where: β – dispersion, MTT – mean transit time. For description of inflow to the brain tissue compartment these

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parameters were $MTT = 4$ s, $\beta = 0^+$ s, $MTT = 6.5$ s and $\beta = 6$ s for extracerebral tissues.

Optical properties of the medium which were applied for the series of simulations were: absorption coefficient of the medium at excitation wavelength $\mu_{ax}=0.015$ mm⁻¹ and at emission wavelength $\mu_{am}=0.005$ mm⁻¹, reduced scattering coefficient of the medium at excitation and emission wavelength $\mu'_{sx}=\mu'_{sm}=1$ mm⁻¹, refractive index $n=1.4$, absorption coefficient of the dye at emission wavelength $\mu_{afm}=0.0001$ mm⁻¹. Thicknesses of the layers: superficial 1 cm, deeper 1 m (which simulates semi-infinite medium). The simulations were carried out for a total of 20 millions of photons for every assumed combination of μ_{afx} in extra- and intracerebral layers of the model. Each single simulation run took no more than 20 minutes on a 2.4GHz PC.

The formula (1) was used to describe inflow and washout of an optical contrast agent in upper and lower layers of the model which reflect intra- and extracerebral tissue compartments during typical measurement of the head (see Fig. 1).

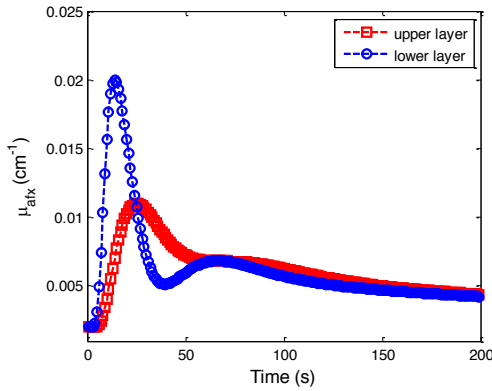


Figure 1. Relation between changes in absorption coefficient of the dye at excitation wavelength μ_{afx} (in lower and upper layers of the two-layered model).

B. Signal processing algorithm

The time-resolved signals of diffuse reflectance and fluorescence were processed by calculation of their two statistical moments: N_R , N_F (total number of diffuse reflectance/fluorescence photons), and V_R , V_F (variance of DTOF and DTA), respectively. Time courses of these statistical moments can be calculated for diffuse reflectance and fluorescence signals recorded during the inflow and washout of the optical contrast agent. The algorithm of data analysis is based on differences in sensitivities of the moments to the changes in absorption located at different depths in the optically turbid medium. It was shown that in diffuse reflectance measurements higher order moments are more sensitive to the changes in absorption coefficient in deeper compartments of the medium [4].

In order to investigate relationship between each of the considered parameters following normalization algorithm was proposed:

$$\begin{cases} A_{NORM}(t) = \frac{A(t) - \min(A(t))}{\max(A(t)) - \min(A(t))} \\ B_{NORM}(t) = \frac{B(t) - \max(B(t))}{\min(B(t)) - \max(B(t))} \end{cases} \quad (4)$$

where: A_{NORM} is derived for parameters decreasing due to inflow of the dye like total number of diffuse reflected photons variance of DTOF and DTA V_R , V_F ; and B_{NORM} was calculated for increasing parameter – total number of fluorescence photons N_F .

A combination of the normalized parameters with potentially highest (variance) and smallest sensitivity to the changes located in lower layer of the model (number of photons) based on moments of fluorescence and diffuse reflectance signals was proposed.

Signal $F_{SIG}(t)$ was obtained from normalized moments of DTAs according to the equation:

$$F_{SIG}(t) = V_F(t) - N_F(t) \quad (5)$$

and again normalized according to the equation (4). Analysis of the shape of $F_{SIG}(t)$ shows a good correlation with the assumed time course of the dye absorption at excitation wavelength in the intracerebral compartment $\mu_{afxINTRA}$ during inflow phase (see Fig.2). Unfortunately, the correlation is rather weak in phase of the dye washout.

Analogously, signal $R_{SIG}(t)$ based on moments of DTOFs was proposed:

$$R_{SIG}(t) = V_R(t) - N_R(t) \quad (6)$$

Finally, signal $I(t)$ related to the inflow of the dye into intracerebral compartment was defined:

$$I(t) = F_{SIG}(t) - q \cdot R_{SIG}(t) \quad (7)$$

where q is a parameter which was a subject of optimization procedure in which it was defined as $q = 0.5$. For this value of q the difference between the normalized signal $I(t)$ and assumed time course of the dye absorption at excitation wavelength in the intracerebral compartment $\mu_{afxINTRA}$ was the smallest.

III. RESULTS

Result of derivation of the signal $I(t)$ corresponding to the inflow of the dye into the lower layer of the model was presented in Fig. 3. Comparison of the obtained signal with the assumed time course of the dye absorption at the excitation wavelength in the intracerebral compartment $\mu_{afxINTRA}$ was also presented.

As it was shown in Fig.2. the analysis based only on fluorescence signals leads to difference between calculated and theoretical curves which was not larger than 20 %. It should be noted that maximum difference is reached after the dye washout phase. In order to obtain a better match between the theoretical and the decomposed signals related to the intracerebral compartment we proposed the algorithm based

on combination of fluorescence and diffuse reflectance signals. It was shown that the signal $I(t)$ fits better to the theoretical signal than the function $F_{SIG}(t)$ revealing only 5% difference between the decomposed and the theoretical time courses.

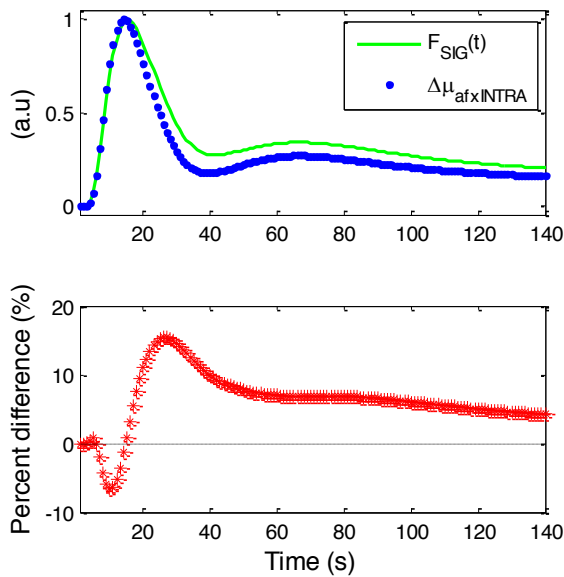


Figure 2. Normalized time course of $F_{SIG}(t)$ and the assumed change in absorption of the dye at excitation wavelength $\mu_{afxINTRA}$. In the second row percentage difference between $F_{SIG}(t)$ and $\mu_{afxINTRA}$ was presented.

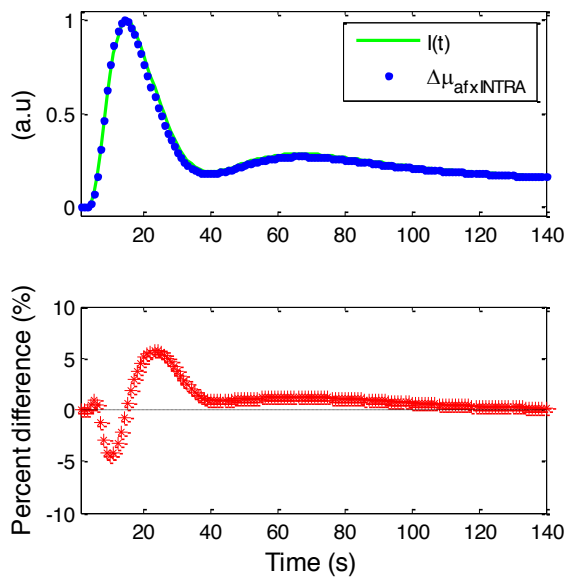


Figure 3. Normalized time course of $I(t)$ and the assumed change in absorption of the dye at excitation wavelength $\mu_{afxINTRA}$. In the second row percentage difference between $I(t)$ and $\mu_{afxINTRA}$ was presented.

IV. CONCLUSIONS

Synchronous measurements of time-resolved diffuse reflectance and fluorescence during the inflow and washout of an optical contrast agent may provide a large amount of data that have not been fully exploited so far. Results of such

measurements may potentially be used for derivation of the components related to the changes in concentration of the dye in the intra- and extra-cerebral compartments of the tissue separately.

In this paper we showed results of decomposition of the simulated signals which was based on four parameters of the DTOFs and DTAs (their statistical moments). It was shown using data from Monte Carlo simulations that estimation of the inflow and washout of the dye in the intracerebral compartment is possible with uncertainty of about 5%. This result suggests that the method proposed can be applied in improved estimation of the brain perfusion parameters based on the bolus-tracking technique.

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