

BIOPHOTONICS

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Application of time gating in the measurement of glucose level in a three-layer biotissue model by using ultrashort laser pulses

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***Abstract*. The efficiency of using the time-of-flight (TOF) method at a wavelength of 820 nm for detecting the changes in the optical properties of multilayer light scattering medium in connection with the problem of the glucose level detection in the human tissue is discussed. Pulses scattered from a three-layer biotissue phantom consisting of two skin layers and a blood layer between them, are calculated with the help of a program code based on the Monte Carlo algorithm for different glucose concentrations. Relative changes in the recorded signals caused by variations in the glucose content are analysed for different source – detector separations. It is shown that the maximum relative change in the total pulse energy is 7.2 % and 4.8 % for the anisotropy factor of the layer mimicking skin $g = 0.9$ and 0.7, respectively, and the change in the glucose concentration from 0 up to 500 mg dL^{-1}. The use of time gating leads to the increase in these values up to 12 % and 8.5 %, respectively. The sensitivity maps are obtained which can be used to determine the optimal duration and the time delay of the time gate relative to the probe pulse for five values of the source – detector separations.**

Keywords: *Monte Carlo simulations, light scattering, ultrashort pulses, time-of-flight technique, time gating, multilayer skin model, phantom, glucose sensing.*

1. Introduction

The problem of non-invasive glucose sensing and monitoring in tissues is one of the main problems in modern biomedical optics, which has been approached with various optical techniques [1–3]. The development of novel techniques and enhancement of the existing ones is stimulated by constant increase in the number of diabetics (more than 170 mln worldwide [4]). The development of noninvasive methods is promising because they eliminate the need for frequent blood sampling to analyse and provide continuous monitoring of the glucose level in human blood [5].

The application of optical techniques for measuring glucose level is based on the fact that variations in the glucose concentration in tissues or tissue phantoms affect their optical properties, in particular, the scattering coefficient μ_s and the anisotropy factor g. These changes are induced by variations in the refractive index n of the medium surrounding the scatterers (in the case of blood, the blood plasma and red blood cells, respectively) [6], which in its turn causes variations in the scattering cross section and the scattering phase function of particles. It was shown in [2, 3, 7] that the glucose level affects the optical properties of tissues in the following way:

$$n = n^0 + 1.515 \times 10^{-6} C, \tag{1}$$

$$\mu_s = (1 - 0.0022C/18)\mu_s^0, \tag{2}$$

$$g = (1 + 0.000007C/18)g^0, \tag{3}$$

where C is glucose concentration in mg dL^{-1}; n, μ_s, g are the refractive index, scattering coefficient and anisotropy factor, respectively, after a change in the glucose concentration; and n^0, μ_s^0, g_0 are these quantities before it.

In recent papers [8–12], such techniques as optical coherence tomography and spatial resolved reflectance (SRR) were shown to be efficient for glucose level monitoring. Time-of-flight technique (TOF) based on detection of backscattered ultrashort pulses in the near IR range can be applied to this problem. In this paper, we analyse the efficiency of the TOF technique for detecting changes in the glucose level in biotissues, particularly, in skin. We also studied the possibility to increase the sensitivity of the TOF method by using time gating.

2. Materials and methods

The propagation of a femtosecond pulse in a three-layer skin phantom (Fig. 1) was simulated by the Monte Carlo method. The wavelength of probe radiation was $\lambda =$ 820 nm. The glucose concentration was varied within the physiological range (from 0 to 500 mg dL^{-1}).

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The Monte Carlo method involves a numerous calculations of the random photon trajectories in a scattering medium and statistical analysis of the data obtained. The specified optical properties of the medium determine lengths and shapes of individual photon trajectories. The results of Monte Carlo simulation of light propagation depend on the choice of a model of the object under study and its optical parameters. However, because the optical parameters of media cannot be measured directly, their values reported by different authors vary significantly depending on the measurement method [13].

We use here a program code of the Monte Carlo algorithm developed earlier in our papers [12, 14–16] to simulate the signals obtained by the SRR and TOF methods. In simulations of TOF signals, the travel time for each photon was calculated simultaneously with its trajectory. The resulting signal represents a distribution of the photons detected by each detector over their travel times, which characterises the response of a medium to the delta-pulse. The output signal can be calculated as a convolution of obtained distributions with the initial shape of the probe pulse. In the case of femtosecond probe pulses, the convolution procedure can be omitted because the typical output pulse duration $\sim$20 ps exceeds the incident pulse duration by several orders of magnitude. In each calculation, 10^9 photons are launched into the medium providing the statistical error less than 0.1 %.

For preliminary approbation of various optical diagnostic techniques a water solution of intralipid at 2 % volume concentration, which is close by optical properties to skin in near-IR range [17], is widely used. Intralipid is a polydisperse suspension of almost spherical particles with a $\sim$ 0.3-μm mean radius suspended in glycerine and water solution. The particles are soybean oil droplets covered with a 2.5–5.0-nm thick lipid membrane [18, 19]. However, the comparison of optical properties of skin and intralipid solution reveals that the anisotropy factors of these two media differ, although the scattering coefficient values are close. In this connection, the simulations are performed for both values corresponding to skin and intralipid. We used a 3-layer skin model consisting of two layers characterised by averaged optical parameters of skin and one layer characterised by averaged optical parameters of blood between them. It was supposed in simulation that the variation in glucose concentration does not affect the optical properties of the superficial skin layer because in human organism the glucose level changes at first in blood followed by change in tissues neighboring blood vessels, while in superficial layer the changes occur later and are insignificant.

The scheme of the simulated experiment is shown in Fig. 1. The embedding depth L_1 of the blood layer is chosen as 100 μm, which corresponds to the approximate depth of the upper plexus in human skin. The thickness of the blood layer L_2 is 200 μm; the thickness of the lower skin layer is 9.7 mm. Thus, the total thickness of the sample is 10 mm, which allows us to consider it as a semi-infinite one. The wavelength of 820 nm is chosen because it lies within the so-called transparency window (600–1300 nm) and is widely used in the noninvasive diagnostics of tissues. Backscattered pulses were delivered to the detectors through five adjacent identical optical fibers with the diameter of 0.2 mm, placed along a chosen axis one after the other on the object surface. The aperture detection angle was 14° corresponding to the typical value for quartz glass.

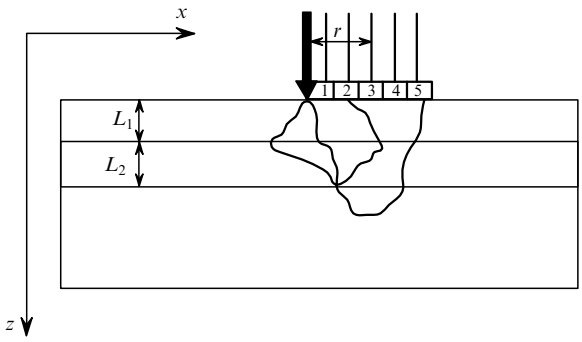

Figure 1. Scheme of the experiment on pulse probing and detection of diffusive backscattering from a three-layer biotissue model. The bold arrow shows the direction and injection point of the probing radiation, 1–5 are the detectors of the scattered radiation.

The normal glucose concentration in the human blood varies in the range from 70 to 160 mg dL^{-1} [5]. We considered variations in the glucose level in the range from 0 to 500 mg dL^{-1}, the lowest and the highest values corresponding to critical states.

The optical parameters of the skin-mimicking layers were chosen by averaging the values reported in papers [13, 20, 21], while for the blood-mimicking layer the values were chosen based on the data reported in [22]. The values corresponding to glucose-free case used for simulations are shown in Table 1. The values corresponding to various glucose concentrations were simulated by varying them according to (1) – (3).

We used in simulations anisotropy factors characterising skin ($g = 0.9$) and water solution of intralipid ($g = 0.7$). Because this parameter strongly affects the character of light propagation in a scattering medium, it is necessary to analyse its influence on the simulation results. Table 1 presents the transport length $l_{tr} = 1/(\mu_a + \mu_s')$ characterising the chaotization of the photon movement direction, where $\mu_s' = \mu_s(1 - g)$ is the reduced scattering coefficient.

Table 1. Optical parameters of the layers used in the simulation ($\lambda = 820$ nm).

Medium	μ_s/mm^{-1}	μ_a/mm^{-1}	g	n	l_{tr}/mm
Blood	57.3	0.82	0.977	1.4	0.468
Skin/intralipid	10	0.002	0.9/0.7	1.4	0.98/0.33

3. Results and discussion

The backscattered radiation intensities calculated by the Monte Carlo method for fibreoptic detectors for two critical glucose concentrations (0 and 500 mg dL^{-1}) are presented in Fig. 2. One can see that for all the detectors the pulse shapes corresponding to different glucose concentrations differ for both anisotropy factors g, which allows one to consider the TOF method as a potential technique for glucose sensing in biotissues. The main difference between the cases $g = 0.9$ and $g = 0.7$ is that in the former case the scattered pulse has one peak, while in the latter case it exhibits two peaks. This effect is explained by the dependence of the backscattering coefficient on the value of $(1 - g)$ of a particular layer, because the mismatch between these values for the skin and blood layers in the case of $g = 0.7$ is significantly larger than that for $g = 0.9$.

For the development of the noninvasive glucose sensing technique implementing TOF measurements one should find the proper quantitative characteristic for estimating the glucose level from the measured pulse shape. In this study, we have chosen the peak value of the measured pulse I, the integrated pulse energy W and energy in time interval $\Delta\tau$: $E = \int_{\tau}^{\tau+\Delta\tau} I(t)\mathrm{d}t$, where τ and $\Delta\tau$ determine the delay and the duration of the time gate, respectively, as parameters which are potentially sensitive to variations in the glucose concentration.

Note that the choice of the peak value as a parameter is not always convenient, because, as one can see from Fig. 2a, for $g = 0.7$ two approximately equal maxima can be present in the detected pulse. Dependences of the peak value and the total energy on the glucose concentration for the first detector for $g = 0.9$ are presented in Fig. 3. One can see that these parameters depend linearly on the glucose concentration; note, however, that the simulation was performed for ideal conditions, while in real experiments the measurement accuracy, possible noises and the limited dynamical range of the measuring system should be taken into account. These dependences for other detectors are similar.

The relative sensitivity of some parameter value to changes in the glucose concentration can be defined by the expression:

$$S_{\text{value}} = \left| \frac{\text{value}(0) - \text{value}(500)}{\text{value}(0)} \right|, \qquad (4)$$

Table 2. Relative sensitivities of peak intensity S_I and integral energy S_W to glucose level variation from 0 to 500 mg dL^{-1}.

Detector number	S_I (%)	S_W (%)	S_W (%)
	$g = 0.9$		$g = 0.7$
1	7.5	5.5	2.9
2	10.9	7.2	4.8
3	10.5	6.9	4.1
4	9.4	6.5	3.0
5	4.5	5.9	1.7

where value(0) and value(500) are the values of this parameter at the glucose concentrations of 0 and 500 mg dL^{-1}, respectively. Values of the relative sensitivities of integrated energy S_W and peak intensity S_I calculated for both anisotropy factors for each detector are presented in Table 2. One can see from this table that the peak intensity is more sensitive to the glucose level, however, this parameter could be used only for $g = 0.9$. In the case of $g = 0.7$, this parameter cannot be determined unambiguously because of the presence of several peaks in the scattered pulse.

If the glucose level is characterised by the total energy W, the maximum sensitivity is achieved at the second detector and is 7.2 % or 0.014 % mg^{-1}dL for $g = 0.9$ and 4.8 % or 0.010 % mg^{-1} dL for $g = 0.7$.

Another quantity studied as a potential parameter was the pulse energy E in the time interval $\Delta\tau$. The idea of this choice is based on the fact that time gating allows distinguishing and accounting only the intervals of the

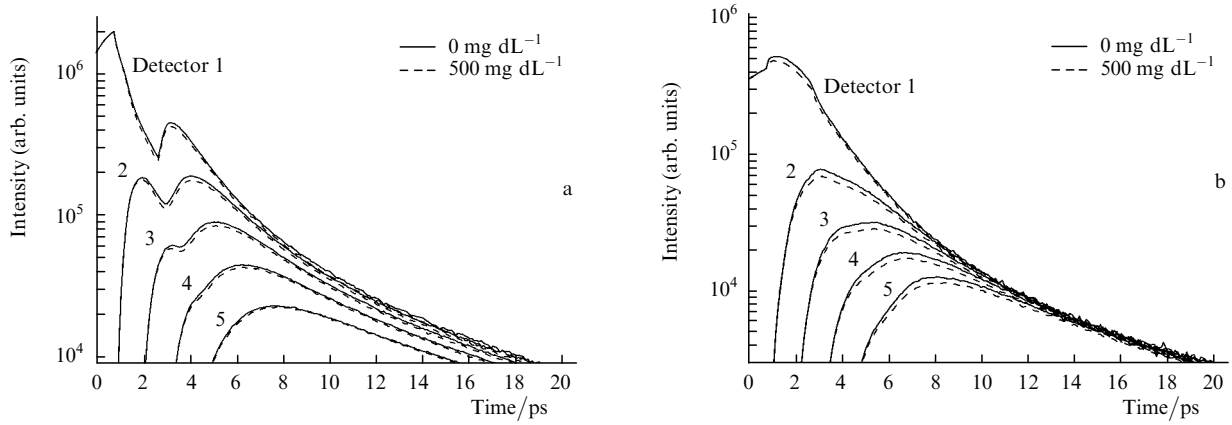

Figure 2. Intensity of backscattered radiation for two different glucose concentrations for $g = 0.7$ (a) and 0.9 (b).

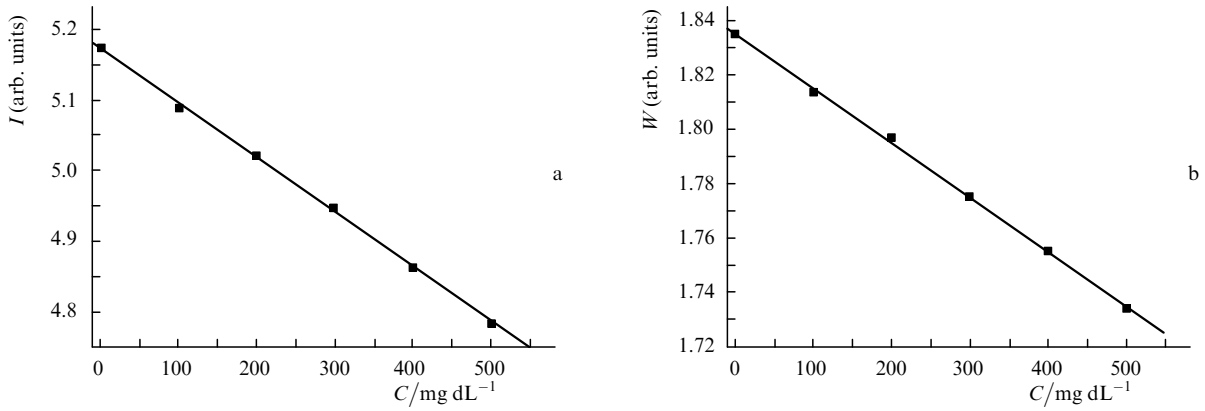

Figure 3. Peak intensity (a) and integral energy (b) of the detected pulses at the first detector versus the glucose concentration C ($g = 0.9$).

temporal pulse profile which are the most sensitive to the glucose level, thus increasing the sensitivity of the technique. The maps of the relative sensitivity S_E of the energy to the glucose concentration change from 0 to 500 mg dL^{-1} at five detectors for $g = 0.9$ versus the delay and the duration of the time gate are presented in Fig. 4. Similar maps are obtained for $g = 0.7$. These maps allow one to estimate the optimal delay and duration of a time gate for provision of the maximal sensitivity. The parameters providing the highest sensitivity are shown in Table 3. For $g = 0.9$ the maximal sensitivity S_E is reached for the 2nd, 3rd and 4th detector for the minimal time gate duration and for time delay of the gate relative to the start of the initial pulse of about 6, 9 and 11 ps correspondingly. In this case the value of S_E is about 12% (0.024 mg^{-1} dL) which is significantly higher than the value of 7.2 % obtained with the pulse integral energy. Similarly, for $g = 0.7$ the maximal sensitivity is 8.5 % (0.017 % mg^{-1} dL) against 4.8 % obtained with the pulse integral energy.

Table 3. Relative sensitivity S_E of energy in time interval to glucose level variation from 0 to 500 mg dL^{-1}.

Detector number	τ/ps	S_E (%)	τ/ps	S_E (%)
	$g = 0.9$		$g = 0.7$	
1	4.2	8.6	5.0	8.0
2	6.6	11.1	6.6	8.5
3	9.8	11.6	8.2	7.6
4	11.2	11.4	9.8	6.3
5	14.4	10.8	11.4	4.5

Summarising the obtained results, one can conclude that the highest sensitivity in TOF measurements can be achieved by using a relatively narrow time gate (duration lower than

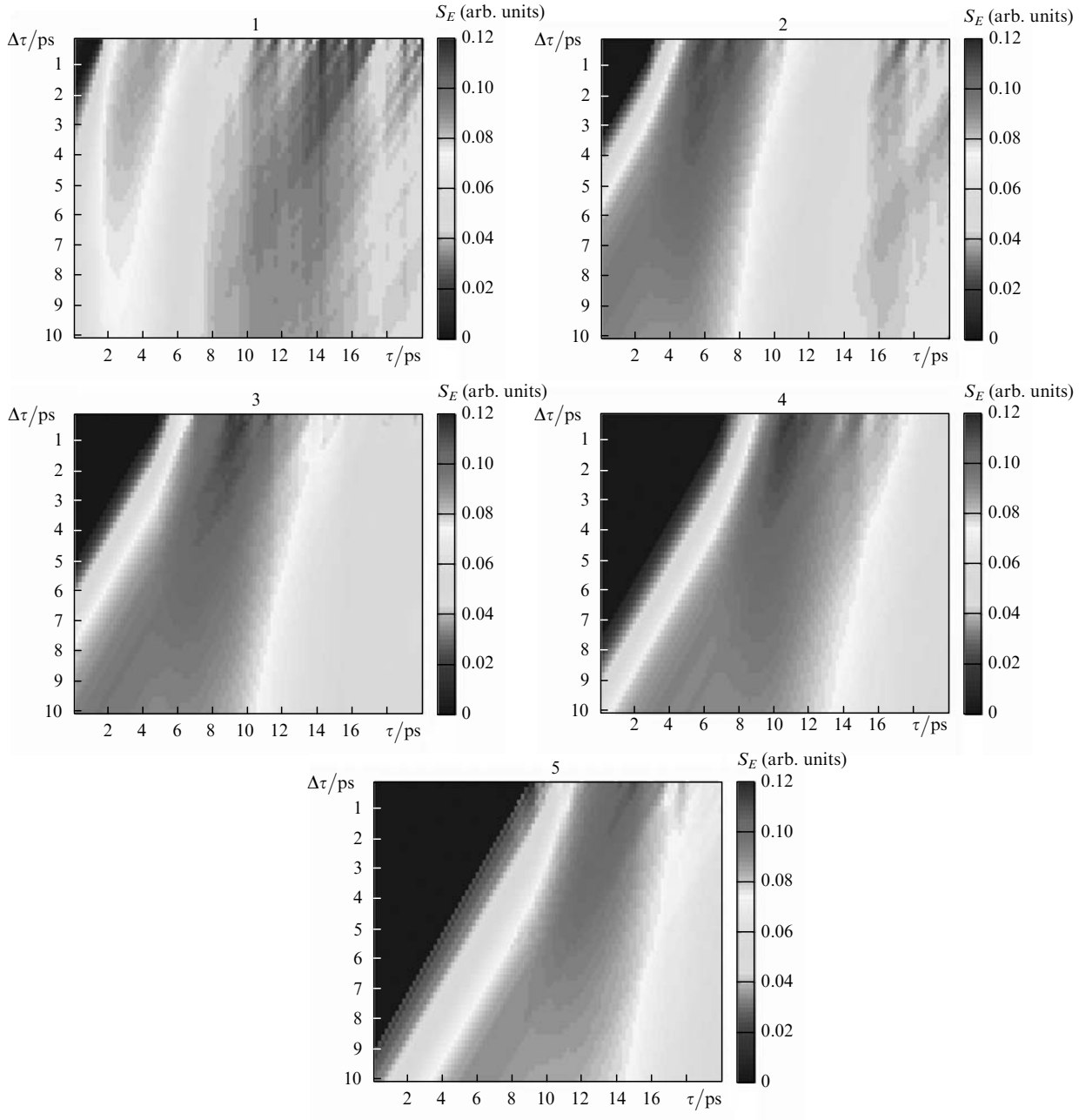

Figure 4. Maps of relative sensitivity S_E of energy in time interval detected at five different detectors (1 – 5) for $g = 0.9$ versus time gate τ and delay $\Delta\tau$.

1 ps) at the second, third and forth detector. The delay of the time gate should be chosen individually for each detector according to the obtained sensitivity maps (Fig. 4). The obtained sensitivities of the scattered pulse energy to the glucose level show that femtosecond laser pulses can be efficiently used in experiments with model and real objects.

4. Conclusions

We have considered the possibility of using the TOF method for noninvasive glucose level sensing in a three-layer human skin phantom. It has been shown that the peak and total energy of backscattered pulses are sensitive to the glucose concentration. The analysis has been performed for five different source–detector separations. It has been also shown that the maximum sensitivity $S_W = 0.014\ \%\ \mathrm{mg}^{-1}\ \mathrm{dL}$ for $g = 0.9$ and $0.010\ \%\ \mathrm{mg}^{-1}\ \mathrm{dL}$ for $g = 0.7$ is obtained for the pulse energy detected at the detector separated by 0.2–0.4 mm from the probe radiation injection point.

We have also analysed the possibility of using time gating to increase the sensitivity of the method. It has been shown that the use of the pulse energy E in the time interval as the parameter provides the increase in the relative sensitivity from $0.014\ \%\ \mathrm{mg}^{-1}\ \mathrm{dL}$ to $0.024\ \%\ \mathrm{mg}^{-1}\ \mathrm{dL}$ for $g = 0.9$ and from $0.010\ \%\ \mathrm{mg}^{-1}\ \mathrm{dL}$ to $0.017\ \%\ \mathrm{mg}^{-1}\ \mathrm{dL}$ for $g = 0.7$. The obtained sensitivity maps allow one to determine the optimal parameters of time gating providing the highest sensitivity.

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