Demonstration of remote optical measurement configuration that correlates to glucose concentration in blood

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Abstract: An optical approach allowing the extraction and the separation of remote vibration sources has recently been proposed. The approach has also been applied for medical related applications as blood pressure and heart beats monitoring. In this paper we demonstrate its capability to monitor glucose concentration in blood stream. The technique is based on the tracking of temporal changes of reflected secondary speckle produced in human skin (wrist) when being illuminated by a laser beam. A temporal change in skin's vibration profile generated due to blood pulsation is analyzed for estimating the glucose concentration. Experimental tests that were carried out in order to verify the proposed approach showed good match with the change of the glucose level at the positive slope stage as it was obtained from conventional reference measurement.

OCIS codes: (030.6140) Speckle; (280.0280) Remote sensing; (170.0170) Medical optics and biotechnology.

References and links

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1. Introduction

Diabetes Mellitus, also known as diabetes is a disease in which one's blood sugar level is high. Today, diabetes is diagnosed by measuring blood sugar level. In addition, diabetics need to be with close supervision on their level of glucose and measure it several times a day [1]. The most accurate method is taking blood samples in clinics and hospitals and giving it for laboratory analysis, however it is inconvenient to the patients. Diabetes can measure their blood glucose level in a less accurate but faster procedure by using a small device that diagnoses blood glucose level by analyzing a small sample of their blood. The downside of this method is that one still needs to pierce himself in order to use the device. Today, all the blood glucose measurement devices must have accuracy following the standards set by the International Organization for Standardization (ISO) [2]. In order to be approved, in 95% of the time the accuracy value must be within the error range of 20%. Most of homely used devices of today have accuracy of 10%-15%.

Directly related with glucose level, insulin is a hormone that regulates energy and glucose metabolism in the body. It affects the liver, muscles and fat tissues causing them to absorb the glucose and store it as a glycogen [3]. The situation of surplus glucose in blood can cause severe complications to human body. It is caused by either pancreas's malfunction, producing low amount of insulin or because the cells in one's body do not absorb the insulin that the pancreas produce.

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Different sensor devices have been proposed for precisely monitoring glucose level while attempting to reduce discomfort produced by the need to extract a small sample volume at low painful body parts such as palm, thigh forearm and abdomen [4]. In that sense, non-invasive glucose meters [5] represent a major breakthrough as the solution to these problems and optical techniques are being in the front of those research efforts [6,7]. The non-invasive optical techniques include: near infrared spectroscopy - a technique that allows tissue investigation in different depths varying from 1 to 100 millimeters [8,9] or 10 to 50 micrometers [10] by transmitting infrared wavelengths, Raman spectroscopy - a technique that measures scattered light that has been influenced by the oscillation and rotation caused by glucose [11], photo-acoustic spectroscopy - a technique that measures an acoustic pressure wave, created by rapid heating of the sampled area [12,13], scatter and polarization changes - techniques that measure the scattering and the polarization properties changes caused by glucose [11,14], femtosecond pulse interferometry - a method for determining the glucose concentration by measuring the group refraction index of a glucose solution using a time delay of femtosecond order in a time-of-flight method with femtosecond pulse interferometry [15,16], optical coherence tomography – a technique based on measurement and analysis of the interference pattern between the coherently backscattered light from specific layers of tissues and a reference beam [17–20], and different types of fluorescence phenomenon [21–23].

In this paper we adjust the basic operation principle of a novel special optical configuration recently developed [24] to monitor level of glucose based on skin vibrations caused by blood flux pulsation. The principle of the proposed special optical setup is to observe the movement of secondary speckle pattern that is generated on top of the human skin (target) when it is being illuminated by a spot of laser beam. We track the temporal shifts and movements of this random pattern reflected from the illuminated skin by performing proper correlation operations [25]. The applied tracking allows determining both the magnitude and the direction of the subject's local surface displacement when properly adapting the optics of the imager as well as the exact image processing algorithm.

Human blood vessels vibrate due to variable (from systolic to diastolic) blood pressure. Human wrist is an ideal spot for blood vessels observation and vibration analysis, especially for heart beats monitoring [25]. Moreover, being in a linear proportion with blood pressure change, vessels movement is suitable for related blood pressure measurements, namely for pulse pressure measurements (the difference between the systolic and diastolic pressures) [26].

Extraction of various parameters from the vibration profile of the illuminated human skin showed that several parameters that are related to the obtained correlation peak can be in a good agreement with the glucose level as it is being estimated by conventional reference measurement when considering the change of the glucose level at the positive slope region, i.e. in the values of the temporal change of the glucose level which starts from the initial level and lasts until the highest level is produced (due to glucose intake by the subject).

In this paper, in Section 2 we present the theoretical explanation, while the experimental results are given in Section 3. Section 4 concludes the paper.

2. Theoretical explanation

Speckle or speckle pattern may be produced in spatially coherent light due to self-interference within the laser beam [27]. The secondary speckle pattern is a pattern that is produced due to roughness of an illuminated surface, while it is constructed on the imaging device plain. The proposed setup is very simple and robust and it consists of a laser and camera which is slightly defocused. The temporal trajectories of the speckle patterns that are captured by the camera are proportional to the temporal signals we wish to extract (a vibration profile of the wrist and of its veins). A self-interference pattern is constructed on the CCD plane of the observing camera. A temporal change in the pattern is related to a relative spatial shift between two

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adjacent frames taken by the camera as was shown before by Zalevsky et al. [25,26]. Using correlation, we extract the relative shift, which is linearly proportional to the tilt of the skin, i.e. the tangent of the angle between the skin surface and the laser projection. Finally, all relative movements are cumulatively summarized for extracting the total movement vector.

The connection between different blood parameters and blood glucose level is explained by L. S. Jefferson et al. in Ref. [3]:

$$C_v(t) = \frac{(1-\varepsilon)\cdot q_0 \cdot h(t)}{F} \tag{1}$$

where $C_v(t)$ is the venous glucose concentration at time t, and F is the blood flow (represents the amount of blood, usually in litters per minute). Glucose pulse is denoted by q_0, it represents the amount of glucose (in mg) in the blood (in Kg) per heartbeat, ε is the fraction of the glucose pulse that is extracted from the blood system and is metabolized, therefore it will never be recovered at the outlet of the vein. h(t) is the reversible fates of glucose in the organ that causes a delay and a distortion in the appearance of glucose pulse in the vein.

If h(t) = 1, the sum of all q_0 is $C_a \cdot F$ and the sum of all $C_v(t)$ is C_v, where C_a and C_v are the arterial and venous glucose concentrations respectively. This assumption follows:

$$\varepsilon = \frac{(C_a - C_v)}{C_a} \tag{2}$$

Thus, the glucose concentration in the arteries and veins is straightly connected to the glucose pulse q_0 and the blood flow F.

A vibration profile of vessel is a unique one. It is characterized by many individual parameters as vessel elasticity, human fat layer, blood viscosity etc. Therefore any change of one of these parameters can distort this profile. Changes in glucose level in blood affect also the viscosity of blood [28], while a change in viscosity of fluid affects the friction between the blood fluid and the vessel walls. Our assumption for capability to monitor the glucose level is based on the fact that a change of friction due to a change in glucose concentration in the arteries and veins causes a distortion of the vibration profile of the vessel.

The developed optical setup for glucose level estimation is capable to measure the tilt of wrist's skin in respect to the projected laser beam. Our aim is to analyze the change in the pulse profile (temporal tilting) by observing quantitative parameters before and after glucose intake and to compare it to the actual glucose level in the blood that is obtained as a reference measurement with conventional techniques.

The relative displacement of the skin due to the change in the shape of the vibrating surface is proportional to the relative shift of the speckle pattern [25,26]:

$$\beta = \frac{4\pi \tan\alpha}{\lambda} \approx \frac{4\pi\alpha}{\lambda} \tag{3}$$

where β is proportional to the relative shift of speckle pattern due to skin displacement, α is the tilting angle of the skin and λ is the optical wavelength. Assuming that the change in the angle is small enough, we obtain a linear proportion between the relative shift and the angle of tilting.

In this paper we show that the temporal change of glucose concentration $C_v(t)$ is proportional to the temporal change of β(t) (which is proportional to the relative shift of the speckle pattern):

$$C_v(t) \propto \beta(t) \tag{4}$$

Therefore, β(t) can be used as possible estimator for glucose concentration in blood.

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3. Experimental results

The constructed system is presented in Fig. 1, where one may see a schematic sketch of the system (Fig. 1(a)) as well as an image of the camera with its optics and a laser illuminating a hand of a subject being fixed by gypsum to allow more accurate measurement (Fig. 1(b)). The setup is very simple and includes only a green laser (at 532nm) to illuminate the inspected object and a camera (having slightly defocused optics) that is connected to a computer. The camera captures images of the secondary speckle pattern being reflected from the hand of the subject at rate of 350 frames per second (fps). The focal length of the optics that had been used in our experiments was 50mm and the distance from the laser to the subject's hand was about 50cm. The laser output power was about 10mW.

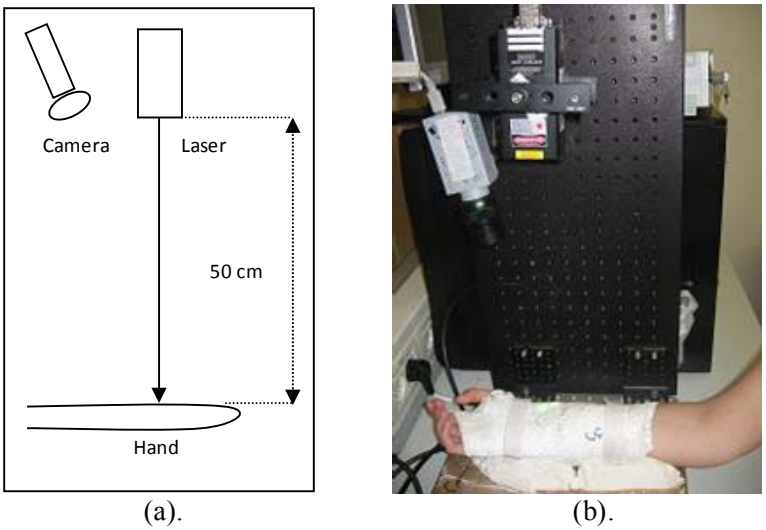

Fig. 1. The implemented optical configuration for remote measuring of glucose level in blood from subject's hand: (a). Sketch of the optical system (b). Subject's hand under laser illumination as viewed by the camera.

After extracting the speckle pattern in each frame we perform correlation and obtain the change in the 2-D position of the peak versus time. In Fig. 2 we show a typical system output with high signal to noise ratio. It includes only several pulses related to heart beating, while in the experiment we take into account the average of six of them. Every pulse is shaped similarly to ECG PQRST [29]. It contains a P pulse, QRS complex, and a T pulse. However, this is a mechanical vibration profile, rather than an electrical signal (as ECG) and therefore it provides us with additional temporal information about vessel's vibration due to blood flux pulsation.

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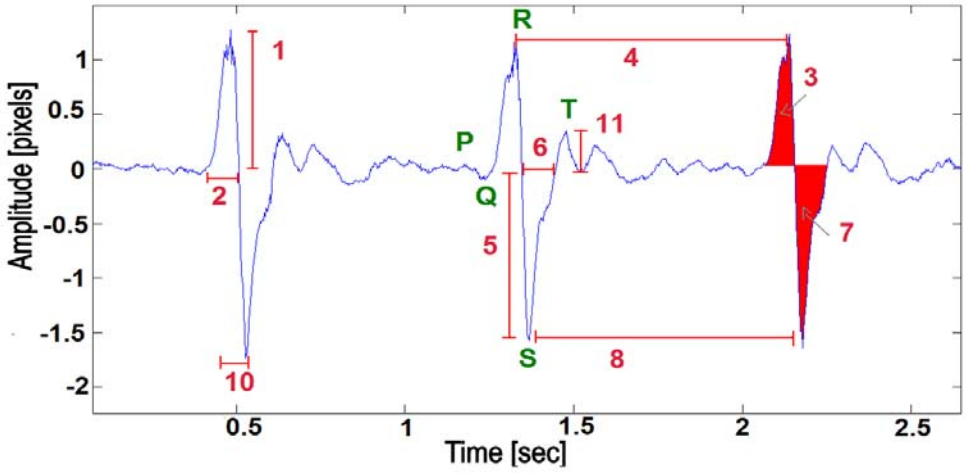

Fig. 2. Temporal plot of the outcome from the system used in the clinical tests with the graphical description of the observed parameters.

In this research, we have chosen to monitor two types of parameters: the first is proportional to the amplitude change and the second to the temporal change of the relative speckle shift. The parameters of the extracted pulse profile that are proportional to amplitude change are: main peak amplitude (positive and negative), pulse profile energy (positive and negative separately), positive to negative pulse peak ratio, secondary peak amplitude and main to secondary peak amplitude ratio. The parameters of the extracted pulse profile that are proportional to the temporal change are: pulse width (positive and negative), mean distance between peaks (gap or pulse rate), distance from positive to negative peak. These parameters are listed in Table 1, while the graphical meaning of them is presented in Fig. 2.

Table 1. Summary of the Observed Parameters

N	Parameter	Units	Comments
1	Positive pulse amplitude	Pixels	Refers to highest amplitude during one heart beat
2	Positive pulse width	Seconds	Estimated between 2 zero-crossing points
3	Positive pulse energy	$(\text{Pixels})^2$	Integral of the enclosed area in the positive pulse profile
4	Gap	Seconds	Number of frames between 2 peaks (pulse rate)
5	Negative pulse amplitude	Pixels	Refers to lowest negative amplitude during one heart beat
6	Negative pulse width	Seconds	Estimated between 2 zero-crossing points
7	Negative pulse energy	$(\text{Pixels})^2$	Integral of the enclosed area in the negative pulse profile
8	Negative gap	Seconds	Number of frames between 2 negative peaks
9	Amplitude ratio	-	Absolute value of the ratio between the positive and the negative peaks
10	Peaks distance	Seconds	Number of frames between the positive and the negative peaks.
11	Secondary peak amplitude	Pixels	Refers to S point of QRS- complex
12	Main to secondary peak ratio	-	Absolute ratio between the main and the secondary peaks amplitude.

Amplitude ratio based parameters (parameters #9 and #12) were chosen in order to perform the experiment with reduced sensitivity to vibrations of the optical setup itself. Those parameters are dimensionless quantities and therefore they are not sensitive to a change in the laser's projection angle.

In order to make the measurements reliable, we needed to be sure that the same spot on the hand is illuminated and examined at every moment. Therefore, an individual hand template was constructed using gypsum, while a hole was drilled into it for each one of the subjects to

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allow the illumination of the wrist (Fig. 1(b)). The diameter of the hole is slightly larger than the laser beam's diameter (approximately 1cm). We have tested four healthy subjects from 22 to 35 years old with different gender and weight. The summary of the subjects' personal information is listed in Table 2. All measurements were repeated several times to assure repeatability and correctness.

Table 2. Summary of the Subjects' Personal Information

#	Gender	Age	Weight
1	Female	22	55
2	Male	22	62
3	Female	24	44
4	Male	35	90

3.1 Calibration tests

In order to authenticate the required accuracy of 10-15% variation (as per standard glucometer) for reliable experiment results, we needed to be able to illuminate the same spot on the wrist over time. We built individual fixation devices for subject's hand using gypsum and executed several check tests. We inserted the hand of the subject, then marked the pulse's spot on the hand, drilled a hole through the gypsum in the position of the chosen spot, pulled the hand out and re-inserted it. The marked spot was at the exact position.

Another test was aimed to check the stability of the gypsum fixation over time. Each subject inserted his hand into the device and stayed fixed for approximately 30 minutes, while he was monitored by the system. In Fig. 3 one can see the stability of the system, while the results do not vary more than 15%. Glucose concentration is shown in units of [ml/dl] divided by 10 (representing a constant level of 100 [ml/dl]), while the units of parameter #6 (please refer to Table 1) are counted in samples.

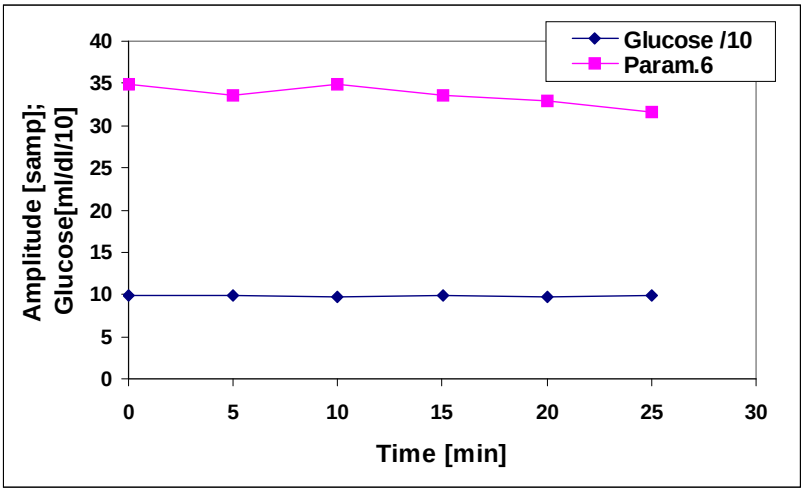

Fig. 3. Stability of the system: constant glucose level in blood (denoted by blue line with triangles) and the estimated parameter 6 (denoted by magenta line with rectangles). Glucose level is given in units of 0.1[ml/dl] (representing a constant level of 100 [ml/dl), while the estimated optical values are given in pixels.

3.2 Main test

To ensure that the glucose blood level would rise only as consequence of drinking of a sweetened beverage during the experiment, each examined subject preserved a fast for about

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12 hours before the measurement took place. The expected values of blood glucose level for non-diabetic person [1] after fasting falls to values range between 90 to 110 [mg/dl]. At the beginning of every experiment we indeed checked that the subject's blood glucose level was at this range, while later the subject received a sweetened drink and the level was changed.

The rate at which the concentration of glucose increases is different for each individual and depends on many personal parameters, like: body weight, metabolic rate, level of insulin in blood etc. The blood glucose level as we obtained after drinking of about 400ml of sweetened beverage (40K Cal) by the subjects was from 150 to190 [mg/dL]. Each experiment lasted for 50-80 minutes, during it the measurements were carried out repeatedly every 5 minutes. Each 5 minutes sampling included capturing six subsequent video files of the illuminated spot and taking an accurate blood sample with a glucometer ("Accu-check") and manual blood pressure measurement using standard sphygmomanometer. All experiments showed that blood pressure have not been changed over the time of the experiment. It is important to check this point in order to ensure that the expected change in the pulse profile is indeed caused by glucose intake, rather than by blood pressure change as was shown previously in Ref. [26].

We wrote a MATLAB program that analyzed the videos and extract the observed parameters from the files. Each file contained about 5 seconds of video samples at rate of 350 fps (frames per second), usually containing 6 pulse peaks. Each peak is processed separately and the chosen parameters are extracted and averaged, therefore representing the average of approximately 30 peaks of pulse profile per each 5 minutes. For each parameter the final graph of the estimated glucose level was produced. Joint graphs of the estimated and the reference glucose level for each one of the parameters and for each one of the subjects were created.

Usually we took into an account only the first samples of the estimated values; the ones when the glucose level is still rising (the positive slope of the graph). Those samples were more reliable due to two main reasons: First is that glucose metabolism mediates changes in biochemistry levels: insulinotropic second messengers, including cyclic nucleotides, inositol phosphates, diacylglycerol and Ca^{2+} [30]. Moreover, biochemistry metabolism in limb is not linear [3], therefore the change in blood fluid viscosity due to biochemistry metabolism is not linear as well. We believe that those metabolic processes initiated by glucose intake in the body cause accumulative change in blood viscosity. With some delay after the initial glucose intake, the additional metabolic processes affect the change in pulse profile which is not directly connected to the actual glucose level change. The second reason is an "exhaustion" of the subject. Although gypsum makes reliable fixation, it is not attached "strongly" enough to the hand and after approximately half an hour of the experiment the subject can produce spontaneous movement which may cause a change in the vibration profile which is not connected to the actual glucose change.

In addition to correlation coefficient, we used root mean square error (RMSE) estimation to quantify the relation between the reference and the estimated data:

$$RMSE = \sqrt{\sum_{i=1}^{N} \frac{(x_i - r_i)^2}{N}} \tag{5}$$

where x_i is an i-th sample of the estimated values, r_i is an i-th sample of the reference values and N is the number of samples. The calculated samples were normalized before applying RMSE estimator in order to obtain the common estimation scale for all parameters.

Dozens of experiments were executed with four subjects in order to present a proof of principle validation. Initial results show a good correspondence of the estimated parameters with the positive slop of glucose level change in blood. However the extensive characterization of the parameters is in progress. There was not found any good correlation between the parameters related to temporal change of the pulse profile and the actual change

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in the glucose level. However, some of the amplitude related parameters showed a quite good matching with the actual glucose change. Some of the obtained results are presented in the following figures.

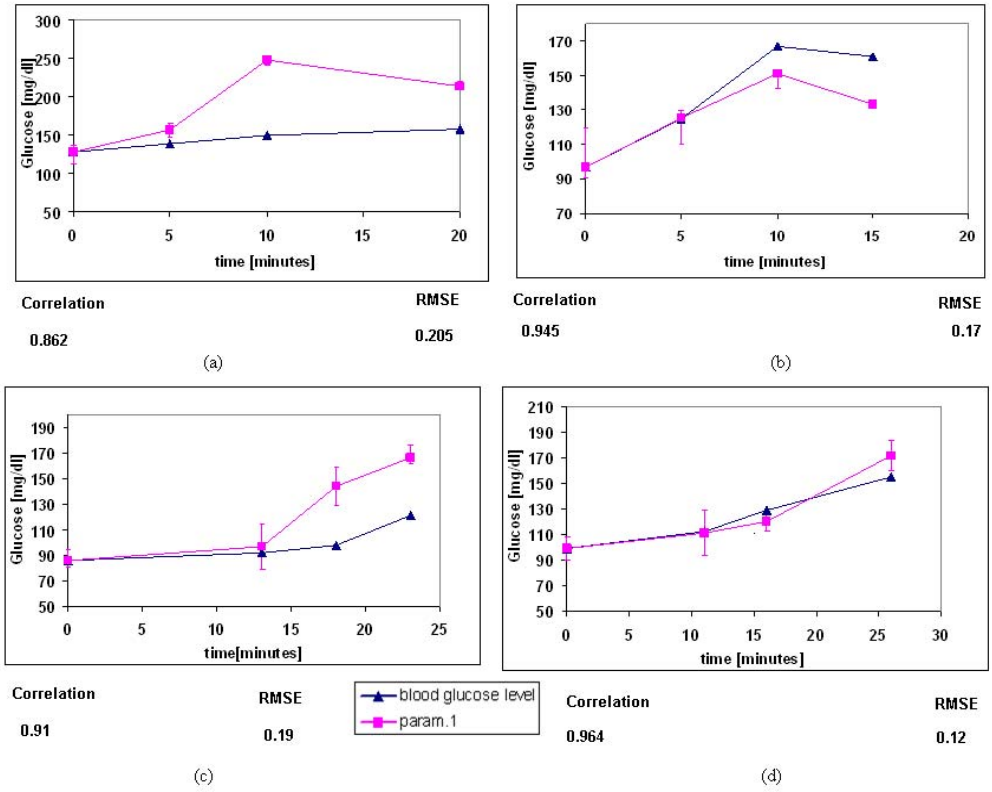

Fig. 4. Data of subject #1: Glucose level in blood and amplitude of positive peak (parameter #1). Glucose level is denoted by blue line with triangles and the optically measured parameter is denoted by magenta line with rectangles.

In Figs. 4–8 we present the temporal evolution of the chosen parameters versus the reference measurement of glucose level taken by glucometer while glucose concentration in blood is denoted by blue line with triangles and the optically measured parameters from the pulse profile is denoted by magenta line with squares. The graph of the reference (glucose level) was obtained by using a conventional glucose meter device ("Accu-check"). Error bars refer to standard deviation of positive and negative deviations separately, calculated over each 30 peak samples (per each point on the graph). Four different graphs on each figure refer to four different experiments taken with relevant subject on different days, during the morning hours while each subject preserved a fast of 12 hours. Estimated values were linearly transformed to glucose level units according to the calibration done per each subject at the first measurement (time 0). Correlation and RMSE coefficients are shown below each graph.

Figure 4 refers to subject #1, while the best correlative parameters for this subject were parameter #1 (please refer to Table 1).

In Fig. 5 one can see graphs taken with subject #1 which show glucose concentration in blood (denoted by blue line with triangles) and the optically measured parameter of the ratio between positive and negative peak (parameter #9) of pulse profile (denoted by magenta line with squares). Figure 5 shows an exact inverse ratio between the estimated and the reference glucose level. Note that parameter #9 is actually a ratio between parameter #1 and #5,

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therefore it is not sensitive to the vibrations of the optical system. Some of the results showed very high correlation with the reference measurement for the full cycle of glucose changes in blood. In Fig. 5(b) one can see that the estimated parameter is tracking after the reference glucose level (in opposite direction). It comprises the positive and the negative slopes, therefore presenting a full cycle of increase and decrease of glucose level in the blood.

The correlation coefficient of −0.916 was obtained between the two curves. RMSE estimator for this parameter was calculated between the inverse function of the normalized estimated parameter (one minus the normalized values) and the reference. RMSE estimator is equal to 0.17 in this case. However, this estimator was working well only for one subject out of four.

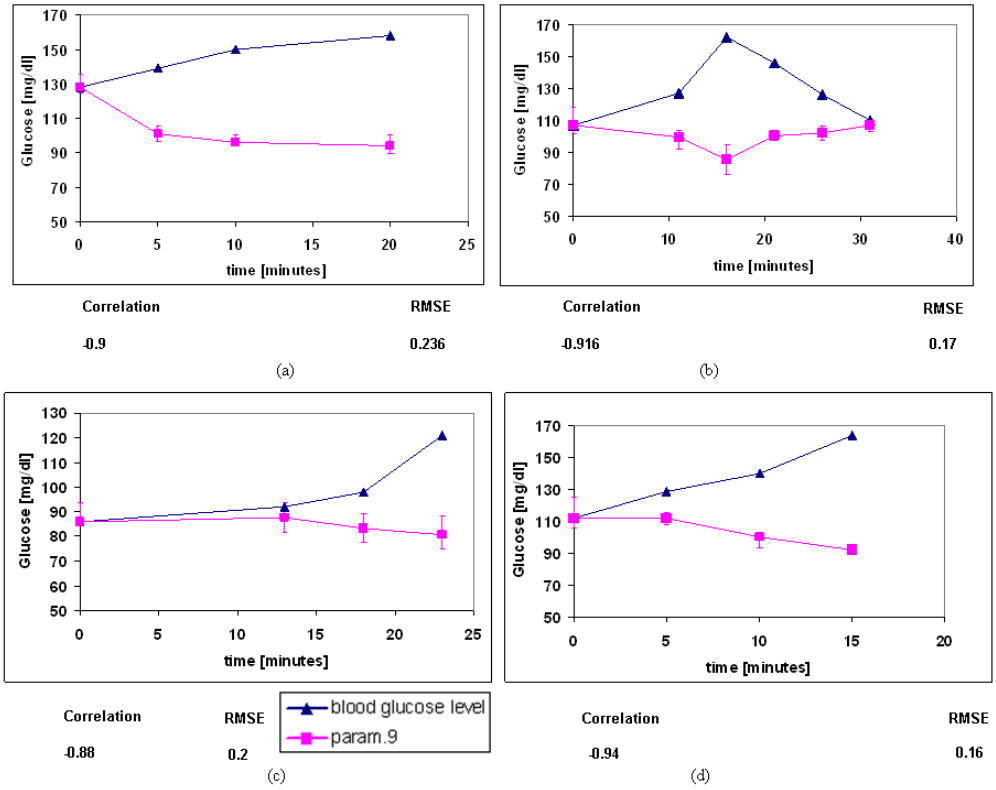

Fig. 5. Data of subject #1: Glucose level in blood and the ratio between positive and negative peak (parameter #9). Glucose level is denoted by blue line with triangles and the optically measured parameter is denoted by magenta line with rectangles.

Figure 6 refers to subject #2, while the best correlative parameter for this subject was found to be positive pulse amplitude (parameter #1). Figure 7 refers to subject #3, while the best correlative parameter for this subject was found to be parameter #1 as well. Figure 8 refers to subject #4, with the best correlative parameter #1.

Table 3 summaries all correlation coefficients, while Table 4 summaries all RMSE estimator coefficients from the graphs presented in Figs. 4–8.

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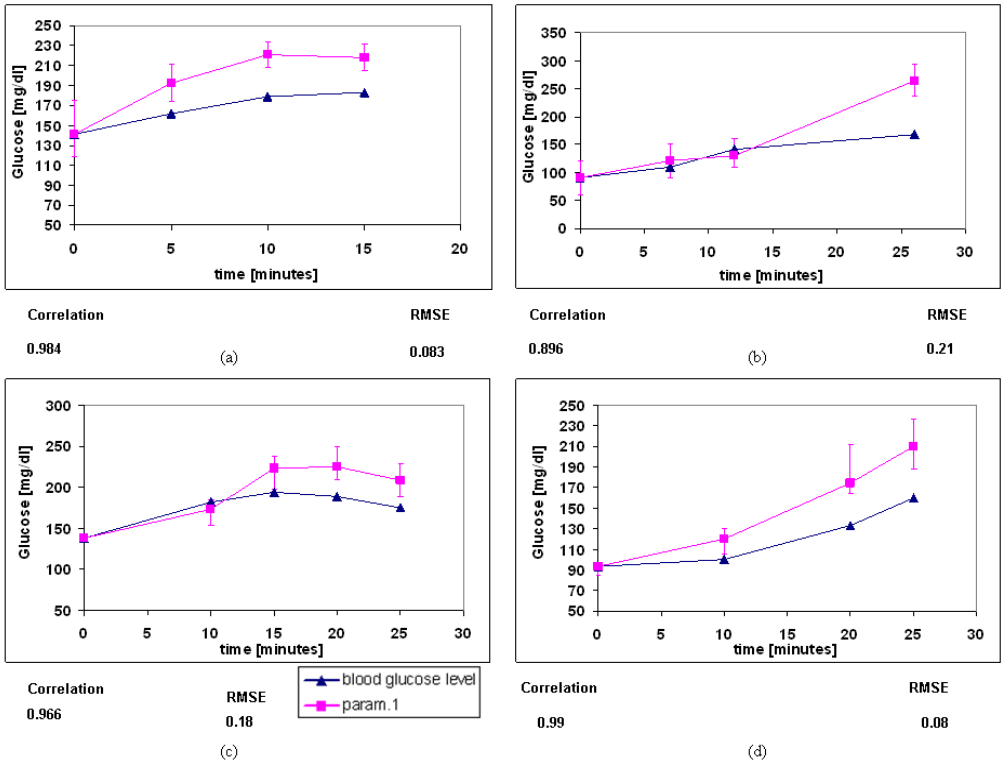

Fig. 6. Data of subject #2: Glucose level in blood and amplitude of positive peak (parameter #1). Glucose level is denoted by blue line with triangles and the optically measured parameter is denoted by magenta line with rectangles.

Table 3. Summary of Correlation Coefficients from All the Tests Taken with the Four Subjects

	Parameter	Test 1	Test 2	Test 3	Test 4	Average
Subject #1	Param. #1	0.862	0.945	0.91	0.964	0.92
	Param. #9	–0.9	–0.916	–0.88	–0.94	–0.909
Subject #2	Param. #1	0.984	0.896	0.966	0.99	0.959
Subject #3	Param. #1	0.99	0.93	0.85	0.943	0.928
Subject #4	Param. #1	0.99	0.88	0.98	0.967	0.954

Table 4. Summary of RMSE Estimator Coefficients from All the Tests Taken with the Four Subjects

	Parameter	Test 1	Test 2	Test 3	Test 4	Average
Subject #1	Param. #1	0.205	0.17	0.19	0.12	0.171
	Param. #9	0.236	0.17	0.202	0.16	0.192
Subject #2	Param. #1	0.083	0.21	0.18	0.08	0.138
Subject #3	Param. #1	0.058	0.18	0.28	0.158	0.169
Subject #4	Param. #1	0.02	0.21	0.08	0.108	0.105

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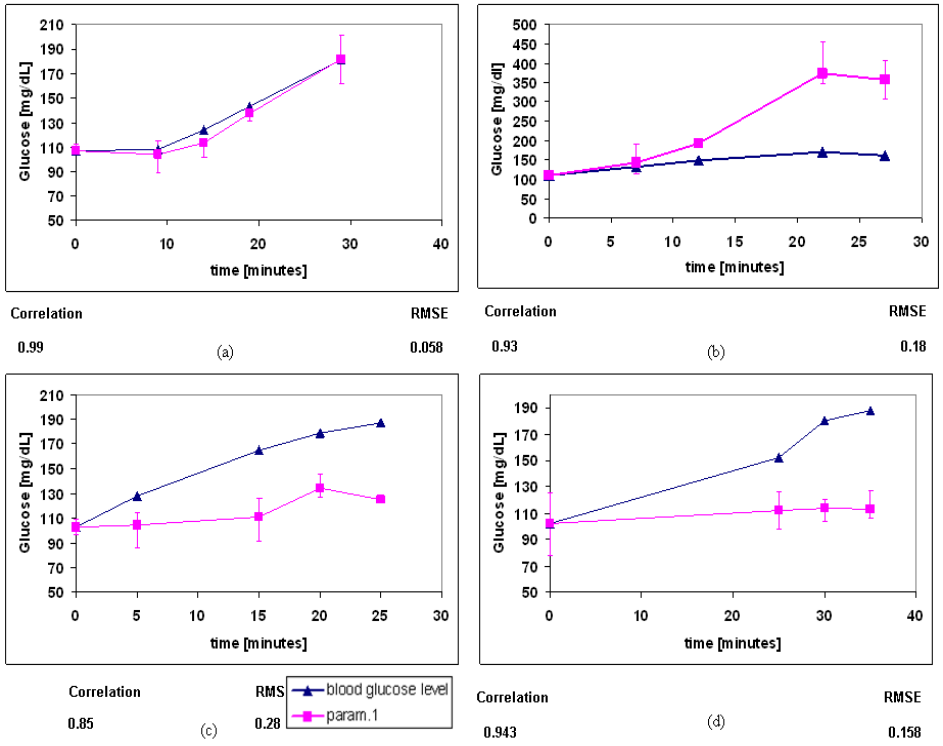

Fig. 7. Data of subject #3: Glucose level in blood and amplitude of positive peak. Glucose level is denoted by blue line with triangles and the optically measured parameter is denoted by magenta line with rectangles.

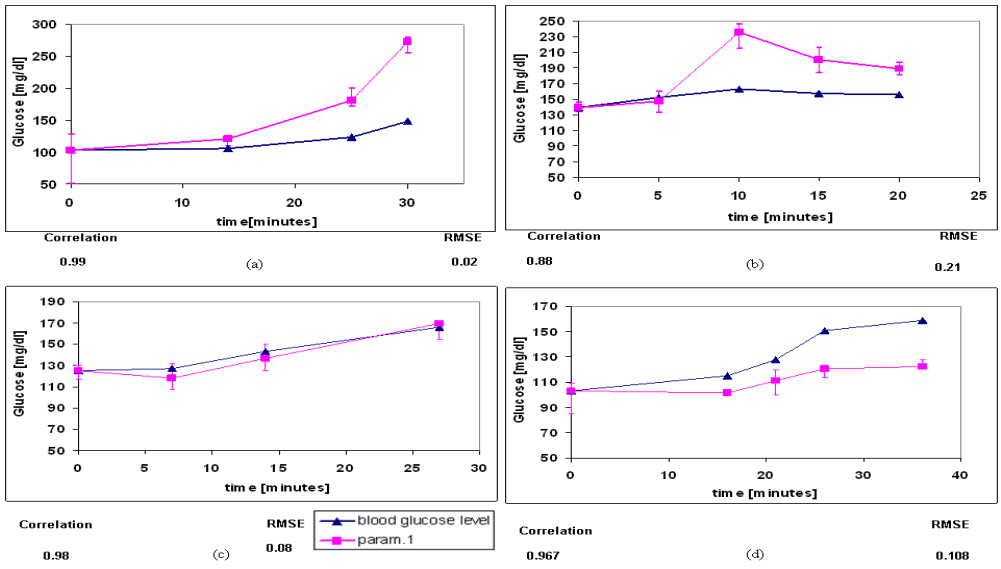

Fig. 8. Data of subject #4: Glucose level in blood and amplitude of positive peak (parameter #1). Glucose level is denoted by blue line with triangles and the optically measured parameter is denoted by magenta line with rectangles.

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4. Conclusions

In this paper we have presented the usage of optical remote configuration for the estimation of glucose concentration in blood. The system was tested with clinical trial group while the estimated results show a high correlation and low error comparing to reference measurement obtained by conventional invasive means.

We were able to demonstrate that a temporal change in the vibration profile of the pulse wave measured from the wrist by our optical technique is proportional to the change of glucose concentration in blood when considering the positive slope, i.e. the positive change in glucose level. Initial results that were collected from dozens of experiments present validation for the proof of principle. However, the extensive characterization of the parameters is in progress.

This new technique means a non-invasive manner of remote measurement of glucose concentration in blood, while it uses only a low power emitting laser and a camera. Further developments of currently presented technology will allow implementation of autonomic and real-time monitoring device, which will be capable of analyzing changes in glucose concentration in blood while allowing free movement of the subject.

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