

A Non-Invasive Method for Spectroscopic Blood Glucose Monitoring

DOI: 10.17691/stm2019.11.2.16
Received June 15, 2018



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At present, diabetes mellitus is considered a life-long condition that has no radical cure. In order to avoid serious complications, people with diabetes have to periodically take samples of their blood "for sugar testing". It is, therefore, obvious how important would be a method for the non-invasive determination of blood glucose. The method proposed in this study is based on spectroscopic measurements of the light passed through a blood-containing organ in the human body. Such methods have been known for a long time; nevertheless, the task of identifying the fraction of light absorbed by glucose remains unsolved. We approach this problem by repeatedly determining the intensity of the absorbed light at multiple wavelengths in the near-IR spectral range; the obtained data are processed using the mathematical tool developed for this purpose, which includes the creation and solution of linear equations with the number of unknowns not less than the number of light-absorbing components in the blood-containing.

The method has been assessed by testing the solution convergence for the system of equations; the requirements for refining the spectral characteristics of some absorbing components have been described.

Key words: diabetes mellitus; non-invasive monitoring; blood glucose concentration.

Introduction

Diabetes mellitus is one of the most common diseases that is currently considered incurable. In order to avoid complications, people with diabetes have to adjust their lifestyle and diet, as well as periodically measure the blood glucose levels. In the case of type 1 diabetes mellitus, they take blood samples several times a day, which is unpleasant and inconvenient. The situation prompted researchers to develop a method for non-invasive determination of glucose in the blood.

At present, there are more or less tangible ideas about the operation and design of such devices that allow avoiding skin puncture. These devices can be classified into two groups: optical and non-optical systems.

One of the non-optical approaches is based on the measurements of organ temperature [1]. It makes use of the correlation between the blood glucose concentration and the difference in temperature between the insulin-dependent and insulin-independent organs. It is known that some organs of the human body can uptake glucose without the assistance of insulin, i.e. those organs are non-insulin dependent. Other organs do need insulin to take up glucose. Under insulin deficiency — as in type 1 diabetes — glucose cannot enter the insulin-dependent organs and thus accumulates in the blood at abnormally high levels. This, in turn, leads to an increased load on

the insulin-independent organs; those start working harder and release more heat, which increases their own temperature. In diabetes, the insulin-dependent organs do not receive sufficient glucose for their function and, accordingly, maintain lower temperatures.

Another non-optical method is based on measuring the level of acetone in the exhaled air, which was shown to correlate with the blood glucose concentration [2].

Also notable is a study of Indian scientists [3]. They propose to determine the level of glucose in the blood using plethysmography combined with electromagnetic verification; the system utilizes multiple sensors. The obtained data is processed using the multidimensional linear regression and artificial neural networks. However, fluctuations in skin moisture and body temperature make it difficult to reach a high accuracy in glucose measurement with this method.

Among non-invasive methods for determining blood glucose, the optical-based approaches are considered the most promising ones [4]. These include photoacoustic, polarimetric, spectroscopic methods, as well as Raman spectroscopy and optical coherent tomography. Spectrometric methods are best-studied; they allow for obtaining information about the presence of various substances including glucose in the blood. Research in this area is quite extensive [5, 6], however, a number of problems remain unsolved.

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Here, we propose a spectroscopic method based on measuring the intensity of absorbed light at specific wavelengths as it passes through a human blood-containing. This principle has been known for a long time [7–9], but so far attempts to identify the fraction of light absorbed specifically by glucose have been unsuccessful. The earlier proposed solutions [7–9] required frequent calibrations against the reference blood glucose measurements; as a result, the accuracy of these techniques was unacceptably low. In fact, they allowed for only a qualitative result showing the glucose level either “close to normal” or “abnormally high”.

In this study, we determine the fraction of light absorbed by glucose using repeated measurements of light absorption at a number of wavelengths in the near-IR region.

A mathematical tool for processing the obtained experimental data has been developed. It creates and solves a system of linear equations with the number of unknowns, which is identical or exceeding the number of light absorbing components in the examined object, i.e. the blood-containing, through which the light passes.

Materials and Methods

The principle for determining a partial light absorption in the blood is based on the Bouguer–Lambert–Beer law, which is expressed by the formula

$$I_0 = I(l) e^{k_\lambda l}, \tag{1}$$

where I_0 is the intensity of the incident light; $I(l)$ — the intensity of light transmitted through an absorbing matter; k_λ is the matter absorption coefficient; l is the matter thickness.

This law is applicable only to a homogeneous matter (more precisely, to a matter that has a measurable thickness). The above equation was, therefore, modified and turned to the following:

$$I_0 = I e^{k_m n_m + k_p n_p + \dots + k_z n_z}, \tag{2}$$

where k_m is the absorption coefficient of the matter of type m at the i -th wavelength and n_m is the amount of the type m matter.

After some transformation, we obtained a simple linear equation:

$$k_m n_m + k_p n_p + \dots + k_z n_z = \ln \frac{I_0}{I}. \tag{3}$$

Thus, for a glucose solution, the formula for the partial light absorption is

$$k_w n_w + k_g n_g = \ln \frac{I_0}{I}, \tag{4}$$

where g is glucose and w — water.

At a specific wavelength, each individual substance has its own absorption coefficient. Since such category as the “thickness” is not applicable to a solved substance, the proposed formula (3) makes it possible to measure the percentage of any substance in a solution.

It is entirely possible that different substances have the same absorption coefficients at certain wavelengths; therefore, we proposed to carry out multiple measurements. As a result, we obtained a number of equation systems. The more systems are produced, the more accurate is the calculation. However, this approach substantially prolongs the time needed to solve these systems, which may become a serious disadvantage. Speedy processing of measurements is not less important than getting results without taking a biomaterial.

At specific wavelengths, some substances have the maximal absorption coefficient, while for others this coefficient is minimal and even close to zero [10]. Therefore, we can neglect the absorption by some substances at specific wavelengths. This procedure significantly simplifies the solution for the obtained systems of equations.

The main test for our mathematical approach is the convergence of the systems of equations. The most common method for determining convergence of a system of linear algebraic equations is the Gauss method — we used it.

In the general sense, convergence of a system of equations is tested by determining the point where the planes intersect. However, in our model, we operate neither with plane coordinates nor with equations of the planes, but with functions, where the values of the absorption coefficient at the i -th wavelength are plotted along one axis, and the intensity of the absorbed light — along the other axis. Since we are interested in the concentration of a substance, which is constant, the functions will converge at one point. Since the system of equations is inhomogeneous (the free coefficients are not zero), we propose to solve it by the Gauss method, that is, by successive elimination of variables. In this method, using elementary transformations, a system of equations is reduced to an equivalent triangular system, where all variables of the system of equations (starting with the latter) are found.

Results

To determine the feasibility of the proposed mathematical model for calculating the proportion of light absorbed by glucose, we conducted experiments with blood samples taken from healthy volunteers at fast and after drinking sweetened tea. The absorption of light at different wavelengths in the visible and near-IR regions up to 1100 nm was measured. The measurements were carried out using a Hitachi U-3410 spectrophotometer (Japan) and a PerkinElmer Lambda 1050 monochromator (USA).

Some of the results are shown in Figure 1.

The obtained values were used for further calculations in accordance with the developed mathematical model. At this step, we selected wavelengths in the near IR range from 700 to 1100 nm (for some absorbing

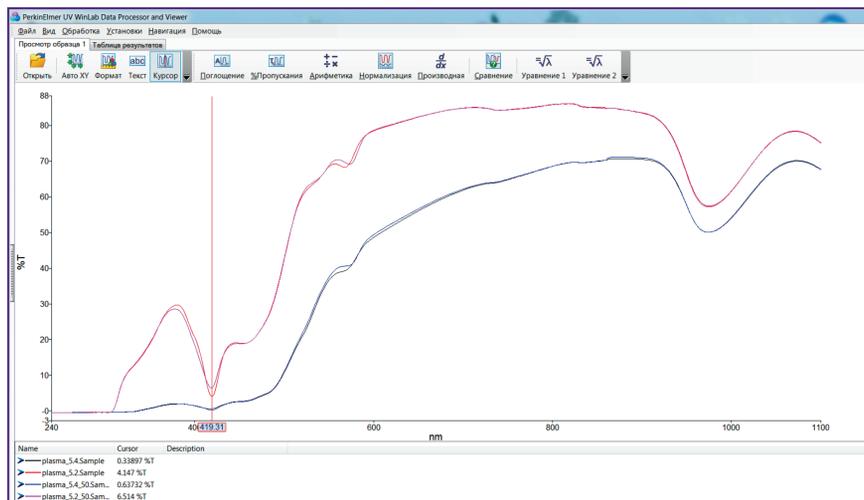


Figure 1. Absorption spectra of the test sample in a cuvette as measured using a PerkinElmer Lambda 1050 scanning monochromator

components, spectral characteristics in this range are rather sharp) in order to eliminate non-essential variables before solving the system of linear equations.

These experiments allowed us to confirm the compatibility of the mathematical model with the selected spectroscopic method. In this model, the results represented the proportion of light absorbed by glucose but not the glucose concentration itself. To obtain the values of glucose concentration (in millimoles/liter), additional calculations were needed. Then, we proposed two approaches.

Approach 1 (based on calculations). To implement it, the following actions should be taken:

1. Determine the approximate fraction of the total absorbing volume occupied by the blood. Statistically, the average value of this fraction can be taken from the literature. We denote this value as δ (a dimensionless number that is significantly less than a unit). As a working fragment of the blood-containing organ, an earlobe can be used [11]. An important advantage of this organ is the absence of bone tissue and the relatively small scattering of the transmitted radiation (scattering is mainly due to proteins). Here, the absorbing components are represented by proteins, water, melanin, the epidermis, and blood components, including glucose. Measurements can be carried out using our originally developed clip shown in Figure 2 [12].

2. Determine the ratio of the glucose volume to the



Figure 2. Measuring clip with input and output fiber optic cables

total absorbing volume. This value will be n_g/δ .

3. Determine the concentration of glucose in millimoles/liter. Here, we accept that the density of a glucose solution is always within 1 ... 1.1 g/ml. Therefore, the concentration of glucose (C) in millimoles/liter can be calculated by the formula

$$C = 10^6 \frac{n_g}{\delta M_s}, \quad (5)$$

where M_s is the molar mass of glucose (180 g/mol). The coefficient of 10^6 includes the conversion of moles to millimoles, as well as milliliters to liters.

Approach 2 is based on calibration. It involves obtaining a calibration value of n_{gc} in

accordance with the proposed mathematical model after the first test of the module; it also involves determining the calibration point of concentration of glucose C_c in the same patient using a reference (invasive) method. The ratio C_c/n_{gc} is calculated and stored in the output glucose concentration program. Then, after each calculation of n_{gc} , the glucose concentration (in millimoles/liter) is displayed on the device interface:

$$C = n_g \frac{C_c}{n_{gc}}. \quad (6)$$

In the present study, the system of linear equations was solved using the Gauss method, that is, by successive elimination of variables. Convergence of the proposed solution is possible if the number of equations (i.e., the number of selected wavelengths) is not less than the number of absorbing components included in the calculations. If there is no convergence, then it is necessary to add more equations obtained from measurements at additional wavelengths. Reaching the convergence can also be facilitated by a set of statistical data resulted from repeated measurements of the intensity of the absorbed light, followed by the calculation of the variance and standard deviation for each wavelength.

Conclusion

The proposed method allows us to calculate the concentration of glucose in the blood based on the determination of the fraction of light absorbed by glucose. By verifying this mathematical model we demonstrate the possibility of creating a non-invasive glucometer based on the developed method. Further research will determine the design of the device.

Research funding. The study was supported by the Ministry of Education and Science of the Russian

Federation (agreement dated September 26, 2017 No.14.575.21.0141, the unique identifier of PNIER is RFMEFI57517X0141).

Conflicts of interest. The authors do not have any conflict of interest.

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