

# Non-invasive blood glucose monitoring with Raman spectroscopy: prospects for device miniaturization

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**Abstract.** The number of patients with diabetes has reached over 350 million, and still continues to increase. The need for regular blood glucose monitoring sparks the interest in the development of modern detection technologies. One of those methods, which allows for non-invasive measurements, is Raman spectroscopy. The ability of infrared light to penetrate deep into tissues allows for obtaining measurements through the skin without its perforation. This paper presents the limitations and possibilities of non-invasive blood glucose monitoring with Raman spectroscopy. Especially focusing on the possibilities for device miniaturization. Such device incorporates a Raman spectrometer, a fiber-optical probe, and a computing device (microcontroller, smartphone, etc.) which calculates the glucose concentration using specialized algorithms. Simplification of device design, as well as turbidity correction technique and a new proposed method of synchronized detection are described.

## 1. Introduction

The number of diabetics in the world equals about 347 millions (in 2013), and is estimated to increase up to about 438 millions by the year 2030. In the EU countries alone, more than 30 m. people suffer from diabetes and over 55 m. in all European countries, according to the International Diabetes Federation [1]. Treatments costs of diabetes and complications resulting from it are estimated to be between 10% and 18% of national health care budgets, especially in the developed countries.

Continuous blood glucose levels monitoring is required for patients with diabetes mellitus to establish the quantity of glucose in blood [2]. Then, the required amount of insulin to be administered is assessed. Widely accepted methods for blood glucose monitoring require sampling of patients' blood and performing measurements on a blood drop. With at least one finger pick per day (and usually three or more) such measurements cause serious health concerns, as well as great inconvenience in patients' daily lives. Complications related to blood draws include weakening of skin which leads to problems with fast healing, risk of infections, pain, etc. Therefore, there is a need to develop new methods, which would allow for continuous, non-invasive detection of blood glucose levels [3].

This papers provides a short review of possible non-invasive blood glucose measurement techniques, with focus on Raman spectroscopy. Furthermore, prospects for miniaturization of such device, based on Raman spectroscopy and subsequent signal processing, is described. A new method, synchronized Raman detection, is proposed to solve the most limiting factor in non-invasive detection, the problem of transferring calibration model between patients due to changes in skin compositions.



## 2. Non-Invasive blood glucose monitoring methods

Currently, the gold standard method for blood glucose detection is the enzymatic reaction of the sample with glucose oxidase to form gluconic acid and hydrogen peroxide, and subsequent readout of the change in current between electrodes on a test strip, or after reaction with oxygen, with a colorimetric readout [4]. A wide range of possible techniques have been applied to the problem of non-invasive blood glucose monitoring, from which we will focus only on the optical techniques.

### 2.1. Fluorescence

Fluorescence is a highly sensitive technique for detection of analytes in general, however, several drawbacks with its application to non-invasive measurements are limited specificity and scattering of tissues [5–7]. Several approaches have been undertaken for blood glucose monitoring, including excitation with UV light and subsequent detection of fluorescence from skin [8], detection of glucose in tears [9], or change in autofluorescence of enzymes, such as NAD(P)H [10].

### 2.2. Optical coherence tomography

Optical coherence tomography detects backscattered light from the samples. Although this method operates mainly in near infrared biological window, allowing for light penetration of about 1 mm into the tissues, it lacks chemical specificity. The scattering changes induced by change of refractive index of the medium due to glucose interfere with other tissue components, thus reducing this method's usefulness [11–14].

### 2.3. Near infrared spectroscopy

Near infrared spectroscopy (NIRS) relies on the measurements of transmitted or reflected light at wavelength in the range between about 750 nm – 2500 nm. This allows for a very deep penetration into the skin, which is use in the measurements of absorption of light by specific molecules [15], as well as in laser therapy applications [16]. This is a widely accepted method for the measurements of oxygenation-deoxygenation of hemoglobin and blood volume pulse known as photoplethysmography (PPG) [17]. The complexity of background spectra arising from the presence of other tissue components (water, hemoglobin, proteins, fat, etc.) is a major obstacle in the development of a NIRS-based blood glucose sensor. Moreover, changes in skin absorption and scattering properties (pigment, disease, etc.) as well as environmental factors play significant roles [5, 18].

### 2.4. Mid-infrared spectroscopy

In mid-infrared spectroscopy (2500 – 10 000 nm range) the effects of scattering are largely decreased, whereas the absorption is greatly increased. Thus, up to a few mm of tissue can be penetrated. Spectral bands of chemical substances are much stronger and sharper, than those in case of NIRS, which permits greater chemical sensitivity. The interference of hemoglobin and blood greatly obstruct the measurements [19].

## 3. Raman spectroscopy

Raman spectroscopy has been previously used for non-invasive blood glucose monitoring, and is most promising due to its superb chemical stability, good penetration depth with near-infrared sources, as well as the amount of developed methods of quantitative data analysis [20, 21]. Raman spectra contain information about the change in molecule energy levels under the influence of laser light irradiation, and subsequent detection of light inelastically scattered from the sample at different wavelengths than the excitation laser wavelength. The difference between wavelengths depends on the specific chemical bond energy. This yields a set of characteristic peaks in the spectrum, which is a "fingerprint" of that specific chemical substance.

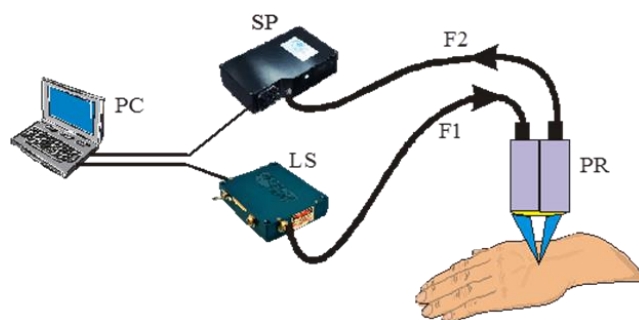
Raman spectra exhibit numerous lines specific for glucose molecular vibrations (Figure 2), such as the skeletal vibrational modes (anomeric  $\nu$  -C-O and  $\nu$  -C-C stretch at carbon #1 at 820–950  $\text{cm}^{-1}$ ,

the  $\nu$  C-hydroxyl and  $\delta$  C-O-H stretch at 1000–1180  $\text{cm}^{-1}$ ) and the  $\text{CH}_2$  vibrations and C-O-H bending at 1200–1500  $\text{cm}^{-1}$ . It is noteworthy that aqueous glucose spectra differ from its powder form.

Application of this method is particularly difficult in the case of biological materials, because of high absorption  $\mu_a$ , and scattering  $\mu_s$  coefficients of tissues (plasma:  $\mu_a \approx 0.03 \text{ mm}^{-1}$ ,  $\mu_s \approx 0.06 \text{ mm}^{-1}$ ; RBCs:  $\mu_a \approx 0.45 \text{ mm}^{-1}$ ,  $\mu_s \approx 30 \text{ mm}^{-1}$ ; skin/tissue:  $\mu_a \approx 0.5 \text{ mm}^{-1}$ ,  $\mu_s \approx 1.2 \text{ mm}^{-1}$ ) [22–24], which causes low levels of Raman scattered signal. Moreover, the random noise, as well as the interference of signals from other substances in the tissues, and strong fluorescence background are another limiting factors [25].

### 3.1. Measurement setup

The basic Raman spectrometer setup consists of components: a laser light source, an optical probe, a spectrometer, and a PC or other data-processing device (Figure 1). The light from a laser source is transmitted through a fiber-optic cable to the optical probe, which contains an optical filter, to select a narrow laser line. Then the laser light irradiates the sample, and the Raman effect occurs, causing the emission of the elastically scattered Raman light back to the probe. The probe collects the Raman light, filters it with a high-pass optical filter, and focuses it on a fiber-optic cable. The light then is transmitted onto a spectrometer where it is split into separate wavelengths and detected on a CCD camera.



**Figure 1.** Laboratory RS setup: LS – laser, SP – spectrometer, F1 – lead-in fiber, F2 – lead-out fiber, PR – optical probe, PC – personal computer.

### 3.2. Detection algorithms

Due to the nature of the Raman spectroscopy, the detected light is often of very low intensity, thus the introduction of random noise is evident, as well as often strong optical instrument background, as well as background coming from fluorescence of the sample. This requires the use of spectral pre-processing techniques and application of de-noising algorithms, background correction algorithms, as well as the removal of cosmic rays and other spectral conditioning methods [26, 27]. In the case of biological samples measurements the amount of noise, as well as inter-patient variability [28] requires use of elaborated multivariate calibration techniques. Complexity of the spectra, and aforementioned patient-to-patient changes in skin optical properties as well as chemical signature, causes largely non-linear response on the examined analytes concentrations, thus the linear methods, such as principal component analysis (PCA) [29] are being replaced by their nonlinear counterparts such as Support Vector Machines (SVM) [30, 31].

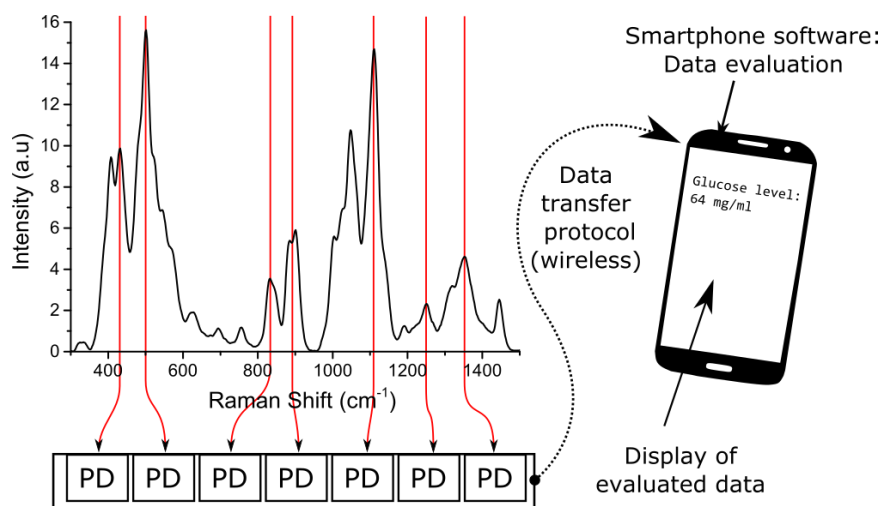
With the advent of these technologies, the weight of the problem of blood glucose monitoring is no longer caused by the measurements itself, but is shifted more towards the data analysis. Thus, the actually achievable measurement precision, and its further improvement, (although still important) seems to introduce less progress and won't bring the ultimate solution of the problem. However, the improvement in data processing will be more valuable and more impactful. Thus, the issue of device miniaturization can be brought to greater attention, when the most of the work remains to be done in the software rather than hardware to make non-invasive glucose measurements a possibility.

#### 4. Prospects for device miniaturization

A vast majority of the Raman studies are performed using benchtop laboratory systems. Such devices are often bulky, stationary, and costly. However, a mobile, miniature RS systems are comparable in their metrological performance to their counterparts [32–34]. With the use of several techniques, it should be possible to allow for further miniaturization of such devices, without the loss in their performance. At the same time, some of the most significant challenges in non-invasive measurements may be additionally overcome.

##### 4.1. Set-up simplification

Upon the identification of spectral bands where the most significant changes are due to the content of investigated analyte, it is unnecessary to measure and process the whole spectrum [35]. It is suggested to focus on those selected areas during measurements, thus to reduced the complexity of a measurement setup by a great deal. First of all, a simplification in the detection setup would require the use of a set of photo detectors and complimentary optical filters in the place of a spectrograph, diffraction grating, and a CCD camera. A miniature IR diode laser modules can be used to reduce space requirements. A schematic of this approach is presented (Figure 2).



**Figure 2.** A schematics of a simplified device set-up, where a set of photodiodes (PD) with band-pass filters replaces CCD camera, and the data analysis and projection can be performed on a smartphone.

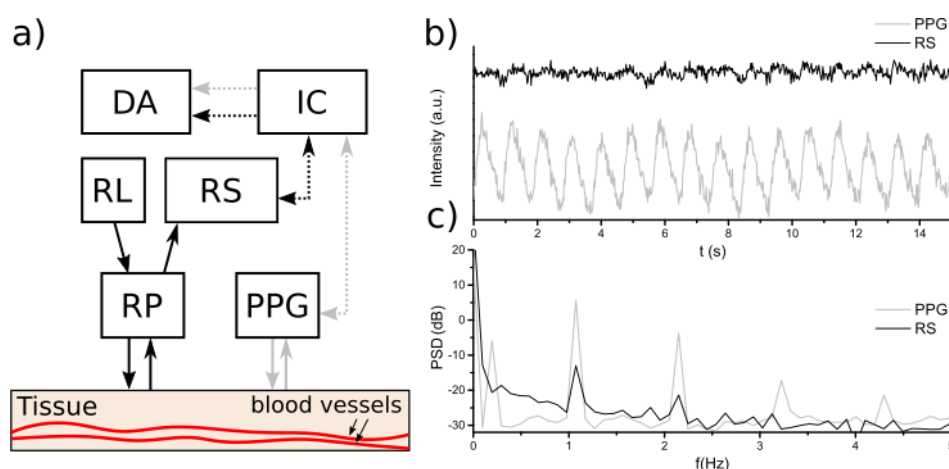
During first experimental analysis, specific Raman band intensity correlated with the change in glucose quantity (here, a sample aqueous glucose Raman spectrum) will be detected using chemometric data processing. For this purpose, Principal Component Analysis (PCA) can be used as an exploratory analytical method. It is possible to detect the bands which carry the informational content related to the investigated analyte, which can be seen on the specific principal components from transformed complex spectra. Furthermore, a PLS-Regression or other more elaborated techniques (PLS-DA, SVM-regression) can be used for quantification. Then, only Raman signal in those selected bands should be detected by a set of photodetectors, such as photodiodes (PD). Then, the received data is transferred to an auxiliary device where the data processing can be performed and the data projected to the end-user; possible devices include: a PC/laptop, microcontroller, or a smartphone. The ever-increasing capabilities and subsequent drop in prices, versatility, as well as a simplicity in use and familiarity for end-users makes smartphone the optimal choice for both a data processing unit and user interface device.

#### 4.2. Turbidity-correction

The biggest issue with the non-invasive blood glucose detection, is the spot-to-spot and patient-to-patient differences in skin optical properties and slight differences in chemical composition. This in turn causes huge errors in the detection algorithms and calibration models, and enable their transfer between. Several methods for the correction of that problem have been investigated, and their performance greatly reduces the prediction errors of multivariate calibration methods. These methods apply a light-propagation model of elastic light scattering, to predict photon migration paths in tissues with various optical properties [36, 37]. Then, upon the measurements of diffuse reflectance at the Raman laser excitation wavelength, as well as the broadband Raman emission wavelength range, a correction factor is derived to minimize turbidity-induced spectral baseline variability [38]. Such approach does not require the use of tissue simulating phantoms (which mimic the  $\mu_s$  and  $\mu_a$  of tissues at specific wavelength range [39, 40]) as well as the knowledge of the absorption and scattering coefficients of tissues for multivariate calibration purposes. However, it is relevant only in a limited range of skin optical properties, but the introduction of diffuse reflectance into the setup is rather simple. Use of this method greatly reduces the prediction error of multivariate calibration techniques.

#### 4.3. Synchronized Raman Detection

Other methods used for the reduction of tissue variability on Raman spectra have been proposed, such as tissue modulation. In this method, the fingertip is gently pressed to later released, to accumulate as much blood as possible in the measurement spot. This results in a "modulated" signal with high and low volumes of tissue blood perfusion [41]. The subsequent analysis proved that both the elastically (laser light and Rayleigh scattering) and inelastically (i.e. Raman) scattered light intensity follows the change of tissue blood perfusion [42].



**Figure 3.** a) Synchronized detection set-up with data flow (optical signals – solid lines), (electrical signals – dotted lines). RL – Raman laser, RS – Raman spectrometer, RP – optical Raman probe, PPG – Photoplethysmographic detector, IC – instrument control unit, DA – Data analysis unit; b) a simulation of Raman signal correlated with blood volume pulse from PPG; c) Power spectrum density of simulated PPG and Raman signals.

Our proposed solution to the problem of individual variability due to tissues could potentially be achieved by application of synchronous detection of optical Raman signal. In this method the Raman signal obtained from a fingertip can be treated as a composition of two components: a DC (or static) and AC (or dynamic) components. The static component contains the Raman signal which originates from the solid tissues (skin, muscle, vessel walls, lipids, etc.), as well as the small amount of blood which always remains in the blood vessels. In other words, it contains the information from the whole volume of irradiated tissue which is stationary in time. The dynamic component originates only from the objects that change with time, that is the volume of blood which is associated with the pulse. Due

to the pumping action of heart, additional amount of blood fills the vessels, changing blood volume at the rate of the heartbeats. In the investigated case, only the dynamic component is of interest, as it carries the Raman spectrum of the blood itself. The static component varies with tissue composition between measurement spots and on a patient-to-patient basis. This causes random and unpredictable changes in baseline, thus the static component can be treated as noise, as it does not carry the informational content. Therefore, the detection of only the AC Raman signal and elimination of a DC Raman signal (associated with the variance in tissue composition) would greatly reduce the prediction error and allow to translate the calibration model to all patients. The synchronization of inelastically scattered Raman signal with the elastically scattered signal from a photoplethysmography (PPG) near-infrared measurement of blood volume, will allow for selection of only the useful (AC) Raman signal. This method can be efficient due to identical scattering properties of red blood cells between people of different age, race and sex. Moreover, scattering on red blood cells is almost two orders more intense when compared with other tissue constituents. The schematic of a system for synchronized Raman detection is presented on Figure 3.a). The Raman detection part comprises of a (RL) Raman laser, (RS) Raman spectrometer, (RP) optical Raman probe. The Raman light will be collected with high temporal resolution, to detect the rapid change in blood perfusion of a tissue, caused by a natural blood volume pulses from cardiac rhythm. Then, simultaneously with the Raman signal, a blood volume signal is detected by a (PPG) photoplethysmographic detector, which is controlled by a (IC) instrument control unit. Both signals from those two modes of detection are transferred to (DA) data analysis unit.

The resulting spectra of our simulations are presented on Figure 3.b). The PPG signal was modeled as a sawtooth/triangle waveform with additional white noise, baseline variability, and additional *dicrotic notch* [17, 43–45]. The resulting Raman signal consists of a DC baseline and a PPG signal with greatly diminished intensity and additional white and pink noise, as well as another baseline variability. The frequency characteristic of these signals were checked with the use of Wiener power spectral density (PSD) presented on Figure 3.c). The PPG signal follows typical spectral distribution of a triangle wave, with basic frequency and power reduced at subsequent harmonics. The basic frequency and first harmonic is retained in the RS spectrum, while the rest of the harmonics is obstructed by noise, and a significant DC component. This preliminary analysis shows, that by application of such method, the inter-patient variability may be overcome, with a simple set-up modification and subsequent software analysis of signals.

## 5. Conclusion

This paper presented current trends in noninvasive blood glucose measurements, with special focus on the Raman spectroscopy. The greatest challenges in the application of this method were described, with the inter-patient variability being the most influential. With the advent of advanced multivariate calibration methods, the weight of the problem of commercialization of such devices lies in the software part, thus permitting their miniaturization. Several signal-processing techniques as well as a set-up simplification were described. Additionally, a new method of synchronized Raman detection, correlated with a natural blood volume pulse was initially analyzed. The frequency response of simulated signals retains blood pulse information. The elimination of individual variability influence on the precision of estimating the blood glucose concentration is a key advantage of the proposed method. Therefore it is concluded that the combination of advanced multivariate techniques, and synchronized detection scheme will solve the inter-patient variability and allow for device miniaturization for commercial purposes. So far such use of a synchronous detection for non-invasive Raman spectroscopy has not been investigated in-depth.

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