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REVIEW

Non-invasive monitoring of blood glucose using optical methods for skin spectroscopy—opportunities and recent advances

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Abstract

Diabetes mellitus is a widespread disease with greatly rising patient numbers expected in the future, not only for industrialized countries but also for regions in the developing world. There is a need for efficient therapy, which can be via self-monitoring of blood glucose levels to provide tight glycemic control for reducing the risks of severe health complications. Advancements in diabetes technology can nowadays offer different sensor approaches, even for continuous blood glucose monitoring. Non-invasive blood glucose assays have been promised for many years and various vibrational spectroscopy-based methods of the skin are candidates for achieving this goal. Due to the small spectral signatures of the glucose hidden among a largely variable background, the largest signal-to-noise ratios and multivariate calibration are essential to provide the method applicability for self-monitoring of blood glucose. Besides multiparameter approaches, recently presented devices based on photoplethysmography with wavelengths in the visible and near-infrared range are evaluated for their potential of providing reliable blood glucose concentration predictions.

Keywords Non-invasive glucose sensing · Vibrational spectroscopy · Photoplethysmography · Color sensing · Multivariate calibration · Validation studies

Introduction

The benefits of tight glycemic control in diabetic patients have been well documented since the completion of the Diabetes Control and Complications Trial (DCCT) studies [1, 2]. Studies indicated that intensive insulin therapy in diabetic patients can dramatically delay the onset of serious complications, and clinical guidelines for management and therapy of diabetes have been published recently [3, 4]. Most diabetic patients are using blood glucose self-monitoring (SMBG) devices for surveillance of their glucose levels and adjustment of their insulin dosage to achieve normoglycemia with glucose concentrations between 3.9 and 7.8 mmol/l (70–140 mg/dl).

Besides the target normoglycemic range, glucose measurement techniques have to focus on an accurate determination of blood glucose concentration when reaching thresholds of the hypoglycemic (≤ 3.9 mmol/l) and hyperglycemic (≥ 7.8 mmol/l) zones, from which on the blood glucose level needs to be adjusted, either by providing an oral carbohydrate intake or with a glucose concentration lowering dosage of insulin, respectively. Other threshold values play a role for diabetes diagnosis, which may be based on plasma glucose criteria, either the fasting plasma glucose (FPG ≥ 7.0 mmol/l (126 mg/dl)) or the 2-h plasma glucose (PG) value after a 75-g oral glucose tolerance test (OGTT) (2-h PG ≥ 11.1 mmol/l (200 mg/dl) using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water. Important for glycemic monitoring is a critical and life-threatening threshold, as glucose concentrations of < 3.0 mmol/l (< 54 mg/dl) will cause defective glucose counterregulation and an impaired awareness of hypoglycemia of the patient.

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Hyperglycemic episodes will lead to an increase in protein glycation in the body including hemoglobin (Hb) in the erythrocytes, as clinically manifested by the HbA1c criterion with values ≥ 6.5% (48 mmol/mol) [4] .

Over the past few years, there has been enormous progress in research to find improved instrumentation for diabetic patients. When undergoing intensive insulin therapy, current monitoring requires diabetic people to prick their fingers for blood sampling several times a day or to use novel continuous glucose monitoring (CGM) techniques, in most cases with implantable needle-type sensors. In contrast to intermittent testing, invasive continuous glucose sensing systems are not yet fully established for optimal glycemic control in diabetic and critically ill patients, to mention another important group with needs for monitoring their glucose concentrations due to drastic and significant disturbance of glycemia.

A non-invasive measurement system would eliminate the inconvenience and pain of frequent blood tests or, as in the case of continuously sensing systems, avoid the invasiveness of needle-type sensors or implanted micro-dialysis catheters in combination with ex vivo glucose sensors. Since the non-invasive methods do not compromise the skin barrier, they could also allow a much higher frequency of readings than using SMBG invasive techniques. However, the assay performance with regard to a required accuracy with absence of systematic and random errors is setting hurdles for everyday applications.

Overview on methods for glucose sensing and fundamental principles

There are various technologies that use different chemical and physical phenomena for measuring blood glucose concentrations. In Fig. 1, we present an overview on currently commercially available or still developed sensor technologies, which can be categorized as being invasive, minimal, and non-invasive. The underlying sensing methods can be categorized into those based on optical techniques, transdermal techniques (involving the measurement of glucose through the skin using either chemicals, reverse iontophoresis, or ultrasound—in contrast to other researchers, we classify those methods as being minimal invasive), electrochemical techniques (mainly with enzymatic detection of glucose in sweat, tears, and saliva combined with, for example, amperometry), and other techniques as bioimpedance (also known as dielectric spectroscopy), which do not fit into the above three general categories. This review will focus on optical sensor systems also still under development. Some papers on non-invasive approaches have been omitted after critical assessment because of inadequate quality with regard to calibration and validation. The optical methods are most promising, as they can utilize different properties of light from the visible to the infrared spectral range to interact with glucose in a concentration-dependent manner: vibrational spectroscopy including mid-infrared (MIR) and near-infrared (NIR), Raman spectroscopy, also with photoacoustic detection, fluorescence, polarimetry (optical rotation), and optical coherence tomography can be listed. Further suggestions rely, e.g., on refractive index changes in the eye, heat capacity measurements, or ultrasonic and electromagnetic techniques. The target site (site of testing) used to measure glucose levels, preferably non-invasively, also differs between the technologies; potential sites include the skin (finger, lip, arm, hand, and ear lobe) or easily accessible body fluids (tear fluid, sweat, and saliva; problems exist with poor correlation to blood glucose).

This is certainly an incomprehensive list; for more details, see report from an extensive literature search published in May 2016 [5], where a total of 40 non-invasive glucose measurement technologies were identified and presented (24 sensor developments were available for intermittent testing, while the residual ones could be used for continuous monitoring). The authors also listed the commercial and non-commercial developers as identified in their search. All but one were being tested in clinical research studies. A final statement was that for many technologies the development is still in the early stages with limited information regarding safety and effectiveness. We actually see most of those developments more critical, concerning especially the devices' safety and reliability of their measurements excluding a few exceptions.

Another rather comprehensive report is from the Institute of Health Economics (IHE) [6], with the subject "Exploratory brief on glucose monitoring technologies." It provides a summary of recently published information (January 2015 to January 2017) regarding glucose monitoring technologies that are commercially available in North America, as well as those that are emerging probably within the next years (up to 2021). The authors cover conventional/traditional glucose monitoring technologies with a special focus on approved and commercially available CGM sensors in addition to some non-invasive glucose monitoring techniques.

Recent overviews on wearable devices have also been published, providing a list of commercialized CGM sensor systems, their features and requirements for functionality [7, 8]. Besides details on current calibration issues for commercial devices given from the same group [7, 9], also approaches to incorporate models of the glucose dynamics between blood and interstitial compartments, important for such invasive sensors, have been discussed. A similar discussion is certainly required when skin tissue integral measurements are used for blood glucose predictions. Overall, the publication provides a splendid overview on the current calibration techniques of CGM devices. With regard to non-invasive methods, two recent reviews should also be mentioned [10, 11]. An informative and up-to-date review has been given by Smith with his book on the many past and ongoing projects devoted to the

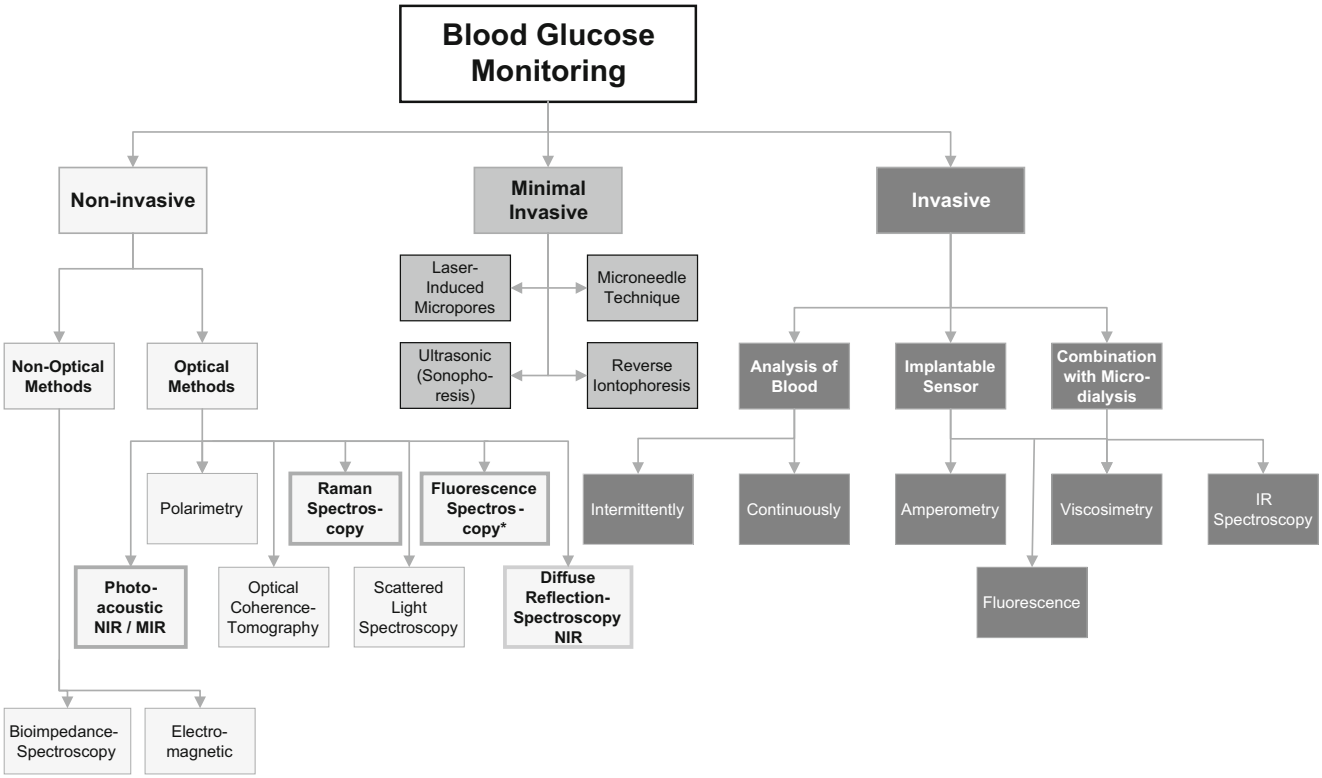

Fig. 1 Overview on the different methods for blood glucose measurement for intensive insulin therapy of diabetic patients (*rated as non-invasive after the implantation of a sensor element)

development of non-invasive assays [12]. A detailed analysis on recently published methods based on skin spectroscopy within the visible and short-wave near-infrared range has been published by us. Our focus was on the assessment of a strategy using color-coded photoplethysmographic imaging of the fingertip for non-invasive blood glucose testing [13].

There are many glucose-relevant physical phenomena, but a problem arises from the difficulty in tracing glucose-relevant information. Direct approaches for analyte quantification usually rely on signals, which can be uniquely related to glucose as existing for the vibrational spectroscopies. This is also the case with enzymatic methods and, e.g., fluorescence for detection based on compounds involved in the reaction that were mediated by the enzyme catalyst (realized by an implanted sensor) [14].

The reliability of non-invasive blood glucose methods can suffer from confounding chemical and physical effects. These can be also physiological factors such as blood perfusion changes, or biophysical property changes of the skin such as a different temperature gradient. Non-glucose-related factors can disturb the measurement significantly, in addition to a poor signal-to-noise ratio of glucose-relevant features, not large enough to allow reliable glucose signal separation. Therefore, many concepts evaluate multivariate data even from multisensor devices. A rather not convincing example for a complex multisensory concept based on dielectric spectroscopy with additional optical, temperature, humidity, sweat, and motion sensors for the detection and compensation of confounding factors has been recently presented by Caduff and Zanon [15, 16].

Chance correlations with instrument drift, noise, or slow physiological changes are a problem with statistical multivariate calibration modeling, e.g., with PLS (partial least squares) or artificial neural networks (ANN), that also requires attention in the validation study design. Oral glucose tolerance tests (OGTTs) or meal tests are usually performed to obtain a large-scale change of glucose levels in vivo. The spectra of an OGTT can only be obtained sequentially in time. If randomized sampling is requested, then consequently the experimental design for calibration will be more complex, for example with glucose clamp experiments aiming at prespecified glucose levels. For the case of slowly changing glucose values, the reliability of prediction results using the statistical regression methods, especially with cross-validation, has been questioned by a number of research workers, e.g., Ref. [17]. Two-dimensional correlation spectroscopy (2DCOS) has been suggested for testing on chance correlations, e.g., from spectrometer drift, sample temperature variations, and interferents. A study presented by Zhang et al. [18] was targeting on the glucose second overtone region with only these three factors being tested (as interferent hemoglobin concentration had been chosen). Other tests such as randomizing the calibration reference values have also been applied to prove the reliability of multidimensional prediction models [19, 20].

For reporting device performances during validation stage, the analytical spectroscopy community uses the standard error of prediction (SEP), which is based on the square root of sum of squared concentration differences, as measured against reference values, divided by the number of measurements. Reference measurements could be provided by commercially available test strip SMBG devices or usually measured by means of Yellow Springs Instrument (YSI) blood glucose analyzers or point-of-care (POC) blood glucose meters. Other numerical criteria provide a testing of the difference between the measured and the reference values such as mean absolute deviation (MAD), mean absolute relative difference (MARD), and median absolute relative difference (MedARD). Clinical evaluation criteria, such as an error grid (EG) analysis [21], assess the clinical accuracy of the glucose measurements in terms of affecting decisions for regulating blood glucose levels in a specified group of patients. The graph provides a scatter plot of a reference glucose meter and the glucose meter under evaluation, broken down into several zones, representing different levels of hazard. The clinically accepted zones are considered to be zones A and B for the consensus error grid [21]. Commercial SMBG devices that meet the ISO 15197:2013 criteria [22] (including a consensus error grid analysis) may show MARD values around 12%, e.g., as shown recently by Pfützner [23]. Interestingly, the impact of errors in self-monitoring had been investigated by an in silico study by Breton and Kovatchev [24]. Valuable information about the relationship was obtained among self-testing errors, risk for hypoglycemia, glucose variability, and long-term, glycemic control. For SMBG errors of 20%, as deviations from the true blood glucose value, for example, incidences of hypoglycemia (with reference glucose concentration values ≤ 3.9 mmol/l) increased from 15 to 22–25.6%.

A wide range of optical techniques has recently been reported for the development of non-invasive methods for glucose sensing based on multivariate skin spectrum analysis [5]. The spectral fingerprints of glucose, either of the mid- and near-infrared or Raman spectrum, have been presented or discussed earlier by one of the authors of this review [25]. A few publications of recent promising work will be presented. For all these strategies, earlier in vitro studies on whole blood, plasma, or serum had shown success for reliable multicomponent analysis with greatest focus certainly on glucose. The glucose assays by mid-infrared spectroscopy of serum or plasma samples had been very successful, but due to strong water absorptions, usually attenuated total reflection (ATR) measurements with transmission equivalent sample layers of 10 μm were favored. Non-invasive measurements would suffer from low photon penetration depth into skin tissue within this region around 1000 cm^{-1} (10 μm wavelength) [26], but with the arrival of quantum cascade lasers as intensive radiation source, new opportunities for in vivo measurements exist. The Raman bands of glucose are rather narrow, which improves the spectral selectivity versus other blood and tissue components, in addition to the fact that water shows a small Raman scattering cross-section when compared to the mid-infrared conditions.

Near-infrared spectroscopy has many options, which are limited by the combination and overtone spectra of water. Whereas combination band region and first water overtone intervals can be accessed with cell pathlengths up to 1 mm (meaning that vascular beds within the dermis can be reached for in vivo skin spectroscopy), the short-wave near-infrared region allows measurements even within a 10 mm cuvette, thus enabling in principle also the trans-illumination of a fingertip. However, as all overtone bands of bio-component spectra become broader, assay selectivity will suffer.

As most published assays were based on near-infrared spectroscopy, we give more details on the glucose spectral fingerprints, on problems caused by water as the main tissue constituent and the sensitivity of the water-hydrogen-bonded network on temperature and solutes such as electrolytes and proteins. In Fig. 2a, wavelength-dependent absorptivities of glucose in aqueous solution and in glassy state are shown (our overtone and combination band data have been compared

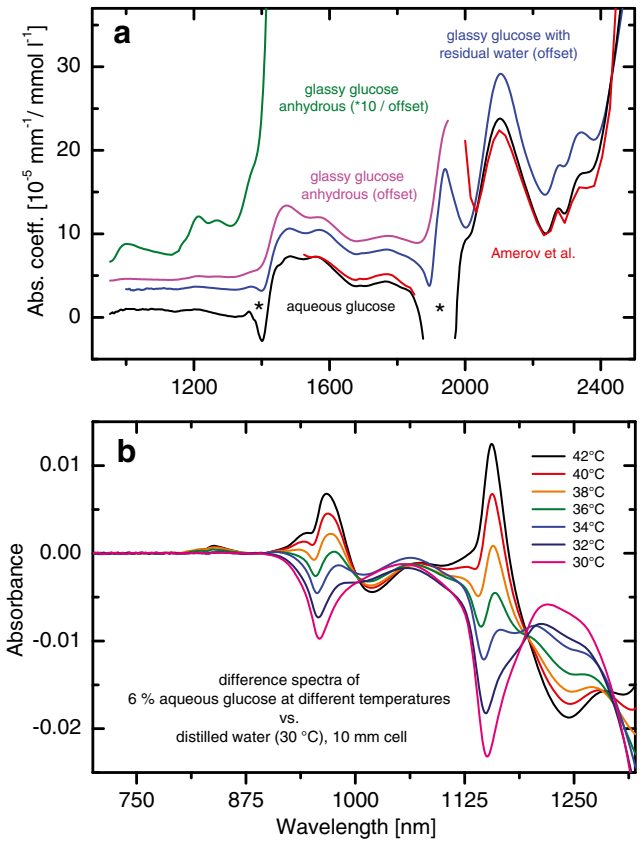

Fig. 2 Absorption coefficient spectra of glucose within the near-infrared spectral range, obtained from aqueous solutions and glassy glucose for extending the spectral range—literature values from Amerov et al. [27] (**a**); aqueous glucose solution spectra showing the dominating water displacement effect and temperature influence on water within the visible and short-wave near-infrared (**b**)

with literature data from Ref. [27]), illustrating already the impact of water, for which perfect spectral compensation is not possible. This is even more evident from Fig. 2b, where the influence of water replaced by glucose and of temperature is illustrated (this is also in view of possible temperature gradients within the skin surface layer; see also Ref. [28]). If the reader is interested in the glucose spectral signatures within the short-wave near-infrared and visible ranges, we refer to publications by Norris [29], Kohl et al. [30], and to our recent review [13]. An overview on the spectral bands of major component spectra is given in Fig. 3, illustrating also their band overlap, which is essential and selectivity-degrading in non-invasive assays based on spectral data within this range.

Raman and mid-infrared studies with fundamental glucose vibrational bands

The use of fundamental vibrational spectra should provide an improved selectivity due to the unique fingerprint spectra,

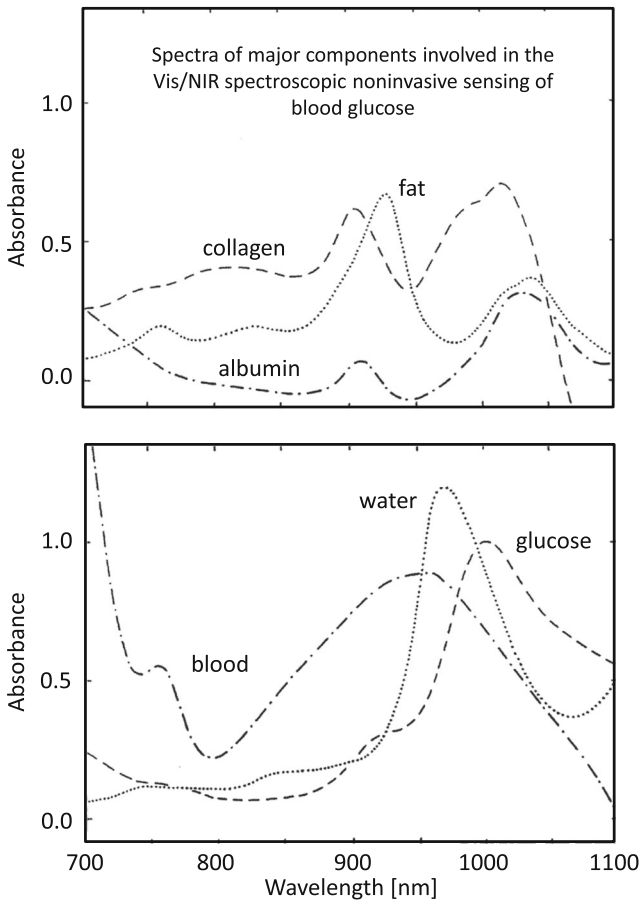

Fig. 3 Skin tissue component spectra recorded within the visible/NIR spectral range, describing opportunities including an estimate of selectivity of non-invasive blood glucose assays, using transmission and reflection measurement techniques (reproduced from Ref. [29], copyright Wiley-VCH, reproduced with permission)

which had been proven in the past by in vitro assays of body fluids by several research groups. Especially, the past Raman work within the mainly involved Massachusetts Institute of Technology (Cambridge, USA), summarized in Ref. [31], must be noted. Their framework addresses issues due to integral tissue probing using a laser diode with 830 nm wavelength, the physiological lag between the blood glucose and the tissue fluid values and non-linear calibration models to account for subject-to-subject variations in skin heterogeneity and hematocrit levels [32]. A pre-calibration step was carried out for transforming the blood glucose concentrations to corresponding interstitial fluid concentrations, while for post-prediction a re-transform into blood glucose values was suggested. Such a concept will work for continuous glucose monitoring, especially for minimal-invasive sensors that probe the glucose concentrations within the interstitial fluid space of the subcutaneous tissue [9], but for integral tissue measurements even more complex modeling will be required (see also below). For more information about the Raman device performance, the reader is referred to citations of earlier publications from this group as listed in Ref. [31].

Another group presented promising results for Raman spectroscopic measurements on a dog's ear, using a diode laser with 830 nm wavelength [33]. Calibration and validation were mainly based on glucose clamp experiments. The spectral regression vector, based on data with glucose values with equilibrium between the vascular and interstitial compartments, also showed similarities to a Raman glucose spectrum. Prediction errors were between ~1.5 and 2.0 mmol/l (27–36 mg/dl) when based on the clamped reference concentration values; these results have been obtained with an elevated average glucose level of 15 mmol/l (~270 mg/dl) for their experiments. Inclusion of the transition intervals between the stable clamp levels, however, led to larger prediction error values, attributed to the physiological lag between vascular and tissue glucose.

With the advent of tunable, room temperature operated quantum cascade lasers for generating intensive mid-infrared radiation, the spectral range around 10 μm wavelength (1000 cm^{-1}), where glucose has its strongest absorption bands, has created great interest for non-invasive glucose monitoring. By using intense, pulsed quantum cascade lasers (QCL) reaching the depth of the dermal papillary loops including the subpapillary plexus is possible for photons of such wavelengths despite the strong water absorption and tissue scattering. Especially with photoacoustic and photothermal detection, results are promising [34, 35]. The advantage of this detection principle is that the volume modulations due to specific tissue component absorptions can be probed without the need to detect backscattered photons above the skin surface. A single measurement took at least 2 min with 20 scans, each taking 6 s. For both principles, leave-one-out root mean squared errors of cross-validation (RMSECV) were

obtained between 0.78 and 1.22 mmol/l (14 and 22 mg/dl), depending on the measurement sites such as forearm, index finger, thumb, or hypothenar. Changes in glucose concentrations were induced by meal uptake. This experimental design is appropriate for the aim of the study to identify an optimal skin site, but direct comparison to the prediction error values from the more rigorous validation strategies, like the Raman spectroscopic study, is currently not possible, although the preceding study [34] also reported spectral glucose features in the glucose regression vector.

Another group around Gmachl employs diffuse reflection spectroscopy by using recently an integrating sphere, but with a focus on finding hardware more suitable for further studies [36]. Their calibration is based on threefold cross-validation on a dataset collected over several weeks with glucose values between about 4.1 and 8.9 mmol/l (75 and 160 mg/dl). Results were presented in an (original) Clarke Error Grid [37] with 78% in zone A and the remainder in zone B. The error grid plots for the three test persons show between 9 and 17 data points each, so one may assume that the measurements were on different days. Unfortunately there is no information, if the daytime for the experiments was always the same. Also important to note are studies by Petrich et al. [38] to determine optical constants of skin within the carbohydrate specific mid-infrared spectral interval. This is essential for modeling the radiation transport for assessing penetration depth into tissue and photon fluence rates.

Coming back to the problem of tissue glucose and blood glucose values for calibration and the transformation of tissue glucose predictions again to blood values, for our early studies [39], delay simulations with equidistant reference blood values were done by application of an impulse-invariant designed Butterworth filter of first-order $y(n) = (1 - e^{-(1/T)})\, x(n) + e^{-(1/T)}\, y(n-1)$ with a time constant of T for aiming at tissue concentrations for calibration, by which the prediction performance of our NIR spectrometric assay with lip measurements could be slightly improved (such an approach could also be tested for non-invasive Raman and mid-IR spectrometric assays). An extended Kalman filter had been developed, e.g., by Knobbe and Buckingham [40] for blood glucose estimates from interstitial glucose values. Further algorithms for modeling the glucose dynamics in both vascular and interstitial compartments have been published, for example by Koutny [41] and Cobelli et al. [42]. The Koutny approach allows an improved blood glucose level reconstruction from interstitial concentration measurements compared to previous two-compartment modeling. For integral skin tissue probing, however, more complex modeling is required, since for an approximation the blood volume fraction, the interstitial fluid space and also an estimate of the intracellular fluid space would be parameters for estimating the glucose amount within the probed tissue. For such calculations, the intracellular glucose concentration cannot be considered as negligible. For HeLa cells, Xu et al. [43] found an average concentration of ~ 1 mmol/l with a relative standard deviation of 43%. This should provide some ideas for integral tissue glucose versus blood glucose measurements. Raman measurements with 830 nm laser wavelength certainly will face a different tissue compartment composition with contributions even from the subcutaneous tissue as mid-infrared measurements, which reach out at the papillary layer and the subpapillary plexus just below the epidermis, for example of the palmar side of a fingertip.

Non-invasive assays based on near-infrared spectroscopy

This section is restricted to studies with a focus on near-infrared spectroscopic aspects of non-invasive glucose sensing (including invasive investigations with relevance for calibration) and is the basis for the following sections, presenting more recent approaches, which additionally employ temporal, spatial, or multisensoric information.

Short wavelengths found within the near-infrared region (780–2500 nm, 12,800–4000 cm^{-1}) provide the opportunity to reach a sufficient radiation penetration depth into skin. There are different accessories available for measuring skin spectra. Fiber-based devices may utilize the geometrical distance between illuminating and detecting fibers to favor the reception of radiation from a certain wavelength-dependent tissue depth (the so-called interactance probes). The photons acceptance angle and thus the collection efficiency, however, is limited by the fibers' numerical aperture. Photons from a wider solid angle can be accepted, e.g., by rotational ellipsoidal mirrors or integrating spheres, which give different average penetration depths and integral photon paths than fiber-based probes [44]. An overview, showing the combination and different overtone regions is provided with Fig. 4a, where results with a fiber-optic probe and a mirror-based accessory are presented; for more details, see also Ref. [45]. Transmission skin spectroscopy is limited in the near-infrared region, even when skin web between thumb and finger is considered (see Fig. 4b).

For better understanding the formation of the non-invasively measured optical signals from tissue, researchers looked at estimations of the influence of glucose in tissue measurements that were based on modeling the radiation transport within the probed scattering tissue volume, with changes in glucose concentration as described by its optical constants (absorption and refractive indices). This can be achieved, e.g., with Monte Carlo simulations of the "photon random walk" based on wavelength-dependent absorption and scattering coefficients. Earlier, still to be reported studies have been carried out by Qu and Wilson [46], who investigated the effect of physiological factors, glucose, and other

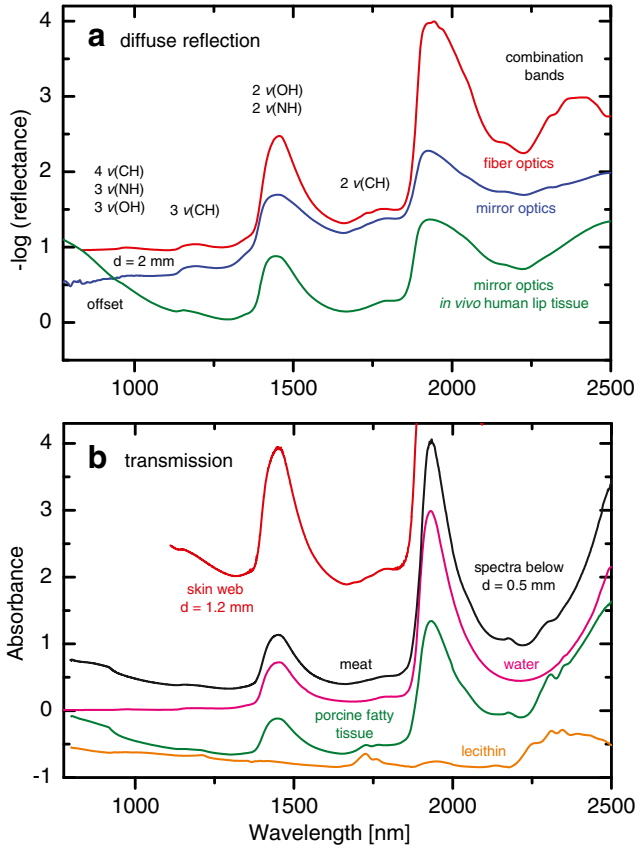

Fig. 4 Near-infrared spectral measurements of porcine muscle tissue of a 2-mm layer thickness and a human lip (photon penetration depth not limited) by reflection using different accessories (**a**) and transmission experiments (lecithin spectrum is shown as an example for the lipid signature as found in subcutaneous tissue) (**b**)

analytes on in vivo measurements by using near-infrared spectral data and Monte Carlo simulations. For this, the optical parameters of tissue, i.e., absorption and scattering coefficients (μ_s) and the scattering anisotropy (g) (the transport scattering coefficient (μ'_s) is calculated by $\mu'_s = \mu_s (1 - g)$) were required. As the refractive index of glucose is higher than that of water, increases in glucose concentration reduce the refractive index mismatch in tissue, thus reducing the scattering and increasing the scattering anisotropy. Also important is the water displacement by glucose, which produces a difference in absorption mainly through water replacement (see also Fig. 2b). Their simulations were done for a collimated incident beam, both transmission and diffuse reflection setups, with a 5-mm-thick slab as sample and for wavelengths of 800 and 960 nm. The optical equivalence for a change of + 1.0 mmol/l glucose concentration, considering the water content, temperature, and protein concentration, was estimated to be + 0.2%, − 0.1 °C, and + 0.1%, respectively, in part due to spectral overlap. For these estimations, the variation of other tissue chromophores, i.e., of hemoglobin (oxy- and deoxy-forms), had not been taken into account (e.g., for 5% tissue blood concentration and 40% hematocrit), which can have an additional significant effect relative to that of glucose.

A simulation of non-invasive glucose measurement by NIR spectroscopy with data between 1200 and 1800 nm was investigated by Tarumi et al. [47] using a Monte Carlo computation for a transmission (2 mm sample thickness) and a diffuse reflection experiment for a semi-infinite medium with an illuminating source (core of 0.8 mm) and concentrically arranged detector (1.8 mm outer diameter). Spectra were simulated with three main parameters only, i.e., glucose concentrations varied between 5.6 and 27.8 mmol/l (100 and 500 mg/dl), the volume fraction of scattering particles (1–5%) affecting the scattering coefficient, and the medium temperature (30–40 °C). The glucose concentrations had an impact on water displacement and affecting the sample absorption and scattering coefficients (through refractive index changes of the solution). The calculated absorbance spectra were used as input for PLS calibration modeling to generate regression vectors for the concentration prediction. The individual impact of scattering or temperature changes onto PLS predictions could so be studied. Based on 150 sample reflectance spectra with −log (R) transformation, prediction errors were within ± 1.1 mmol/l (± 20 mg/dl) (it was not clear if errors had been calculated and reported for the calibration set or if cross-validated values were obtained; usually the standard error of calibration is smaller than the standard error of prediction by cross-validation, especially with ill-posed linear equation systems from similar and noisy calibration spectra) [48]. Anyway, as the Monte Carlo modeling used a very limited set of parameters providing some lower limits for the prediction errors, calibrations with real spectral data will face more confounding factors, thus providing even a larger variance in non-invasive glucose testing.

A glucose absorption coefficient spectrum in the visible and short-wave near-infrared was published by Kohl et al. [30], with the intent of modeling its influence on spectral tissue measurements. Here, the effect of scattering and absorption of a tissue simulating phantom in transmission (optical pathlength of 20 mm), using absorption coefficients of water and glucose including their refractive indices, was studied by applying diffusion theory for photon transport. Experimental phantom data had been provided in conformity for a sample with zero and 200 mmol/l glucose concentration with up to 4% relative change in transmittance for spectra below 930 nm. As a concentration of 5 mmol/l for the normal blood glucose level is to be stated, a reduction factor of 40 needs consideration. This would account for a transmittance change of 1‰ due to the presence of glucose at physiological levels and even smaller deviations for the concentration changes which a device should be able to resolve. This assumption is for an optical pathlength of 20 mm and under the optimistic strategy that linear downscaling is possible.

Due to the small spectral signatures of the glucose hidden among a largely variable background, multivariate calibration techniques based on wide spectral intervals (often in combination with beneficial variable selection schemes for variable number reduction) are required to provide the selectivity and precision for self-monitoring of blood glucose. An assessment of NIR-spectroscopic approaches with a discussion of selectivity and chance correlations has been given by Arnold and Small [20], which is still appropriate for describing problems and pitfalls. If widely used statistical calibration techniques such as partial least squares (PLS) are applied, additional problems can occur like overfitting, unspecific response, or the incorporation of spuriously correlated spectral variance into a calibration model. Noteworthy here are the publications from the group around Arnold with successful experiments using a rat model and transmission measurements through a skin fold, providing SEP values of 3.8 mmol/l (68.5 mg/dl) and 1.98 mmol/l (35.68 mg/dl), the latter with taking into account the estimated time shift of glucose concentration changes between blood and interstitial fluid [49, 50]. For proving the model selectivity, the so-called net analyte signal (NAS) as chemometric approach has been suggested [20, 50]. Interestingly for lessons to be learned, the impact of tissue heterogeneity on non-invasive glucose measurements has also been investigated [51]. Spectroscopic assay pitfalls owing to overfitting, when calibration is based on too many variables and unsound model validation, have also been illustrated by Heise et al. [19]. Here, another useful definition for calibration selectivity has been given, based on a different multivariate calibration strategy called science-based calibration (SBC, outside chemometrics known as Wiener filtering), which requests as input for modeling a clean analyte "response" spectrum and the covariance with confounding contributions and noise. The SBC method is demonstrated for a dataset of transmission spectra in the overtone and combination band region in the long-wave near-infrared from (invasively) collected blood plasma, originally presented in Ref. [52].

In vivo results for non-invasive glucose sensing from our group were obtained with diffuse reflection measurements of lip tissue, based on different multivariate calibration techniques [19, 44, 53]. Latest results were published in Ref. [19]. As most useful spectral intervals, containing important glucose fingerprint signatures, the so-called combination and overtone near-infrared regions were identified. Physiological aspects have also been discussed in detail [44]. These were pressure effects, skin temperature gradients (minimized by standardization of the measurement conditions), skin tissue blood volume, and blood flow changes. The latter were found important for thick skin as given for the palmar fingertip skin with many arterio-venous anastomoses controlling the total blood flow and acting as short-cut valves between larger diameter vessels, thus avoiding the subpapillary plexus. Furthermore, the complexity of calibration modeling has been analyzed by a principal component analysis of the skin spectra recorded over weeks and over a minute scale. Main factors can be related to water spectral features, depending on temperature and solutes.

A different approach in evaluating diffuse reflection spectra of human forearm skin between 1350 and 1850 nm has been presented by Maruo and Yamada [54], based on a modified Beer's law, assuming that absorbance difference spectra versus the first series spectrum can be modeled by a linear combination of water, protein, glucose, and fat spectra and a baseline for scattering equivalent absorption. In principle, this is a classical least squares (CLS) approach, but with evident deficiencies brought away by an additional so-called imaginary spectrum. This is a constructed spectrum that replaces some component spectra and is in the end based on expert knowledge (the imaginary term does not refer to complex numbers here!). The construction process was guided by the finding that gradual changes in scattering within the skin occurred during the continuous patient measurements, which affected the prediction performance because of the similarity of baseline and glucose spectra. As reason for the baseline alterations, a change in skin water concentration due to the sensor placement was identified that does not depend on glucose uptake. So it was possible to introduce a time-dependent "imaginary" spectrum for baseline compensation; time zero was the time when the probe was attached to the skin. Since the method measures glucose concentration changes in tissue only and compensates probe placement effects, it requires an invasive measurement of the absolute glucose concentration when the probe is attached to the skin. Two experimental runs with glucose intake and duration of up to 3 h including individually adjusted background spectra were presented in the article. The first run provided an SEP of 0.5 mmol/l (9.9 mg/dl) while the second experiment showed an example with an SEP of 1.5 mmol/l (27.7 mg/dl), where the described prediction model failed for the first hour, indicating there is additional work needed to identify further influencing factors.

Studies with shorter wavelengths have been carried out but yielded inconclusive results [55]. There, the NIR short-wave region from 700 to 1100 nm has been used to measure the reflectance from a finger employing a so-called interactance fiber-optic probe with illumination and detecting fibers arranged radially, but with at least 5 mm apart. With the latter fiber-optic probe various skin tissue spectra had been recorded while performing an OGTT. Cross-validated results on the palm skin were 0.5 mmol/l (9.7 mg/dl) or with 30 s time difference between invasive and spectroscopic testing an error of 0.7 mmol/l (12.5 mg/dl), whereas model solutions of bovine serum albumin and glucose prepared by factorial experimental design, with added milk for inducing an appropriate scattering were measured in a transmission cell (in test tubes with inner diameter of 17.6 mm), obtaining prediction errors of 2.2 mmol/l (39.6 mg/dl)! Own experiences with short-wave

near-infrared spectra and blood plasma also show that because of broader absorption features for all blood constituents, the selectivity for glucose prediction will suffer with the consequence of significantly increased uncertainty for glucose prediction, similar to the just mentioned value, compared with calibrations using the overtone and combination band region in the long-wave near-infrared [52]; this reference is still providing clinical chemistry landmark results.

As wearable instrumentation is advisable, a miniaturized spectrometer development is required. Recently, a group around Bae [56] presented a miniaturized device that utilized LEDs emitting between 1500 and 1800 nm radially arranged around a single photodetector for detection of backscattered photons. By operating the LEDs sequentially in pulsed mode, the detector receives a sequence of overlapping spectral features from the sample. A spectrum with equidistant variables was mathematically reconstructed (by regularized matrix inversion). Preliminary experiments produced a root mean square (rms) noise of 5 μA.U. (absorbance units) for the first overtone region (for definition see Fig. 4a), but the spectral features show some systematic deviations and also look more smoothed (possible by the reconstruction procedure), compared to the reference spectra from a (bulky and expensive) conventional device.

Wavelength-dependent and time-resolving photoplethysmographic studies

For all integral tissue measurements, the problem exists that the SMBG tests or with blood samples taken by health care professionals blood glucose concentrations are delivered as reference values for comparison. The optimal information for the patient is actually provided with arterial blood glucose concentration, which can be considered as the "gold standard" for glycemic testing. Techniques such as photoplethysmography (PPG) utilize time-resolved optical measurements for accessing chemical information from the vascular compartment. They have been successfully applied for pulse oximetry, providing the arterial blood oxygen saturation by quantification of oxy- und deoxyhemoglobin. Both components are photometrically accessible within the visible and short-wave near-infrared spectral ranges (Fig. 5a, which also provides data for skin melanin compounds; downloaded from https://omlc.org/spectra/), where fast and highly sensitive silicon-based sensor technology and light-emitting diodes at different center wavelength are available at affordable costs. In Fig. 5b, tissue spectra recorded with a fiber-optic probe (with random arrangement of fibers for illumination and detection) are shown for finger and lip tissue, in addition to a water absorbance spectrum at 5 mm layer thickness. Visible light or infrared radiation reaching the detector in either transmittance or reflectance mode has passed different skin layers,

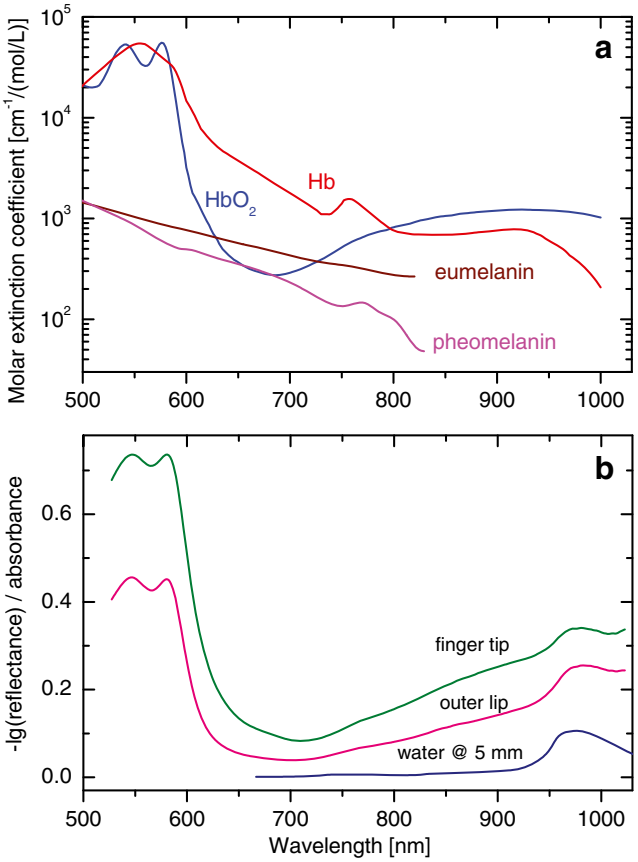

Fig. 5 Fundamental optical data for blood and skin constituents in the visible and short-wave near-infrared (**a**) and diffuse reflectance spectra of integral lip and finger tissue by a fiber-optic probe; also given is a water absorbance spectrum for a sample layer of 5 mm, measured in transmission (**b**)

each imprinting its spectral signature in a pathlength, material, and geometric-dependent manner (see paragraphs on radiation transport modeling in the section above). In Fig. 6a, a schematic photoplethysmographic signal, based on a basic partitioning in arterial, venous, and tissue compartments is shown. With time resolution in the subsecond range, it shows a large direct (DC) component attributed to tissue, venous, and in part arterial absorption or scattering and a small alternating (AC) component. The latter originates from several cardiac synchronous vascular factors including changes of blood volume, blood-vessel wall movement, and the variable orientation of red blood cells in vessels [57] mainly assigned to changes in arteries and arterioles, due to the blood pressure changes with each heartbeat. This small AC signal is the main PPG signal and is measured for two or more wavelengths.

Furthermore, there are superimposed lower frequency components on top of a slowly varying baseline attributed, e.g., to respiration, vasomotion, sympathetic nervous system activity, and thermoregulation. However, there is evidence that in contrast with the classical model, photoplethysmographic waveforms also originate from the modulation of the dermal capillary density caused by the

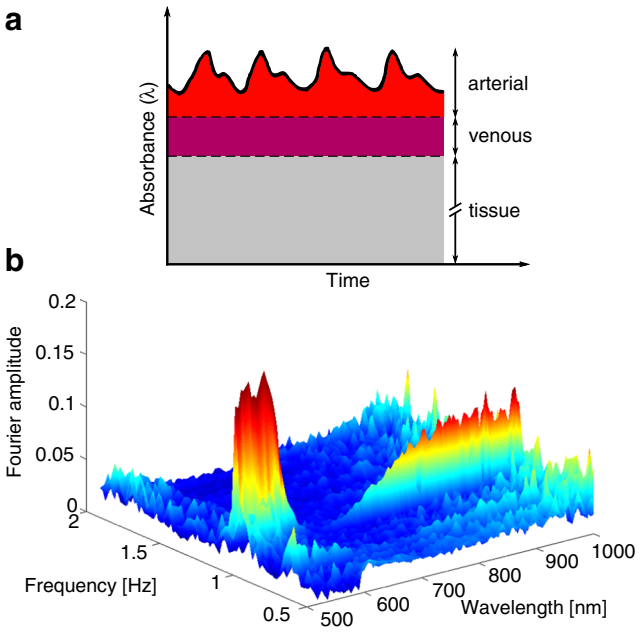

Fig. 6 Schematics of the wavelength-dependent photoplethysmographic signal (**a**) and pulsatile spectrum at heartbeat frequency from subsecond lip spectra obtained by an integrating sphere (**b**); for details, see the text

pressure variations from the larger blood vessels below [58]. An interesting publication with the anatomy of the vascular systems in the cutaneous and subcutaneous areas is given by Sangiorgi et al. [59].

Concerning the PPG waveform recorded from the fingertip, an overview can be obtained from Elgendi [60]. Its appearance is divided into two phases: the so-called anacrotic phase is the rising part related to the systole, whereas the catacrotic phase is the falling edge with diastole and wave reflections from the periphery. A dicrotic notch is usually observed in the catacrotic phase of subjects with healthy compliant arteries. The author also listed several physiological (e.g., local hypothermia) and pharmacological factors (e.g., from vasoconstrictors such as noradrenaline), which influence the systolic amplitude. Low-amplitude pulse wave tracings may be due to poor finger perfusion resulting from hypotension from a number of causes including distributive or hypovolemic shock, hypothermia, use of vasoconstrictor agents, and poor cardiac output due to pump failure or dysrhythmia.

Now, we come back to the in vivo spectroscopy of skin. The same approach with time-resolved subsecond spectroscopy had also been chosen by us for time-resolved lip measurements within the near-infrared spectral range with water as the main chromophore. First results had been reported, e.g., in Ref. [53] for wavelengths above about 1000 nm. There are complications arising from the blood as a non-Newtonian fluid, which means that its viscosity changes as a function of shear rate. When blood moves quickly as in peak-systole, it is physically thinner; when it moves slowly during end-diastole, its viscosity is increased, also because of red cells aggregation. Spectral variance effects are expected for the hydrogen-bonded network of the water surrounded by plasma proteins under different flow regimes. The wavelength-dependent pulsatile components from lip tissue spectra below 1000 nm recorded with 250 ms time intervals and an integrating sphere are shown in Fig. 6b, which were calculated by Fourier transformation of the time series signal at each wavelength variable, providing also the heart beat frequency and the corresponding Fourier coefficients.

Yamakoshi et al. also started similar work with spectra between 900 and 1700 nm and called this pulse glucometry. In 2015, experiments were carried out by using an integrating sphere, but a more advanced set-up for side-scattered finger photoplethysmography was presented in 2017 [61]. First, they compared PPGs with three wavelengths: 808 nm, 1160 nm, and 1600 nm (with nearly peak glucose absorption and strong water absorption), while the source-detector spacing was successively increased circumferentially around a fingertip. Second, with this arrangement, an experiment was performed using six wavelengths to cover glucose absorption bands (from 1550 to 1749 nm), obtaining pulsatile PPG signals with more or less 15 dB of signal-to-noise ratio. Their statement is that potential for practical measurement of arterial blood constituents including glucose exist, which needs further work.

Another optical approach based on pulsatile measurements in the short-wave near-infrared spectral range with LEDs at 935, 950, and 1070 nm, where glucose shows absorption features, was followed by Ramasahayam et al. [62]. The group described a low-cost, portable device for continuous blood glucose sensing, which employed signals from photoplethysmography. Glucose concentration prediction was via an artificial neural network (ANN) after preprocessing the time-dependent signals by neural network-based adaptive noise cancelation filter (adaline) for motion artifact reduction based on a triaxial accelerometer signal. After ANN training the network including its weights was implemented on a field-programmable gate array (FPGA). Clinical trials were carried out on 100 subjects with Clarke error grid analysis and 95.4% within region A, which covers predictions with 20% deviation to the reference values and all residual values were found within region B. Assuming that the clinical trial used the fixed FPGA implementation of the ANN, the validation test set was independent from the training set. An interesting and from our point of view relevant contribution has been made by Monte-Moreno reporting on a non-invasive assay for blood glucose and blood pressure based on photoplethysmography [63]. Here, the PPG signal had been recorded with a fingertip pulse oximeter device iPod Digital Oximeter using light-emitting diodes (LEDs) at 660 and 925 nm (according to a specification sheet from year 2005) and facing a photodiode, while blood glucose measurements were done using a self-monitoring blood glucometer Accu-Chek Aviva. A signal processing module extracted features from the PPG waveform and a

machine learning algorithm of either implementing ridge linear regression, a multilayer perceptron neural network, support vector machines, or random forests regression was used for calibration. The method does not measure differences in time intervals or in light absorption, but exploits the effect of physiological changes on the shape of the PPG waveform and on the heart rate. The author claims that these measurements are related to the subject's hemodynamics and the blood glucose level. A total of 4500 measurements within 1 min duration were recorded. Preprocessing is for motion artifact elimination, before a vector of time-dependent features is extracted. As physiological factors, relevant for the method, blood viscosity and vessel compliance have been listed and claimed, while blood viscosity is mentioned to rely also on both blood pressure and glucose concentration, altering the flux of blood in the capillaries and the shape of the PPG pulse.

As for example the metabolic syndrome causes changes in glucose and blood pressure levels as well as the general hemodynamics, it was required to add individual's variables such as age, weight, and body mass index in addition to pulse shape [63]. Also mentioned is a functional relationship between altered glucose levels due to diabetes and heart rate variability. Another confounding factor can be the emotional state, affecting blood pressure and glucose concentration, correlated with heart rate variability and the spectral PPG shape. For taking breathing and effects from the autonomic nervous system into account, low frequencies of the PPG signal have also been considered. The system performance based on the coefficient of determination (R^2) was rather poor (< 0.64) unless random forests regression was applied. Final results were achieved with data from 410 subjects with a tenfold cross-validation, i.e., 90% of the data was used for training, leaving 10% for testing with 10 times rotation ($R^2 = 0.90$). A test for overfitting was included, which consisted of training with a random permutation of the reference glucose values. Those results showed that the system was not able to predict glucose concentrations from permutated and thus meaningless reference values ($R^2_{\text{training}} = 0.017$).

Photoplethysmographic studies amended by spatially resolving sensor technology

Recently, two publications on the performance of a novel non-invasive blood glucose meter called TensorTip Combo Glucometer (CoG), developed by Cnoga Medical Ltd. were published by Segman [64] and Pfützner et al. [23]. The device has a folding compartment for the finger that is illuminated by four different LEDs in the visible red and short-wave near-infrared. Photons will traverse from the tip through skin and tissue to an image sensor under the finger pad, which is taking up the side-scattered radiation, similar to the finger photoplethysmography set-up as described in Ref. [61]. The image sensor has three color channels and a measurement takes about 30 s [23], but no information about its resolution, frame rate, and optics, if applicable, is given. Segman mentions that changes in blood flow and color pigmentation were to be detected, requiring a large dynamic range (number of bits per pixel) and a high frame rate per second. The underlying interrelation to blood glucose levels and confounding factors have not been investigated. The device seems to rely purely on a calibration versus invasively measured reference values that is achieved by a so-called neural brain network (NBN) with vague or no information on the architecture and the input and output layer. In a previous stage of development (studies 1 and 2 [64]), this calibration was universal (calibration data from many different patients, used to predict glucose for different individuals), while in the current stage (study 3 [64] and standardized meal study [23]), an extensive personal calibration of at least 25 invasive blood reference measurements (56 recommended) is required, taking at least a week even for tight glucose management plans. The device also requests recalibration measurements for somehow out of range non-invasive measurements and based on an individual, not further specified "calibration structure."

Concerning the device performance, the percentages within zones A and B of the consensus error grid [21] have been mentioned for two clinical studies (1 and 2) with 76 and 77 patients, respectively. Percentages were as follows: 81% (A) and 19% (B) (study 1); 88% (A) and 12% (B), while a third so-called home study 3 reached similar results [64]. A standardized meal study [23] provided a MARD value of 14.4% with CEG zones A (96.6%) and B (3.4%), which are the best performances so far reported.

Due to the existing, but weak absorption features of glucose (see also Refs. [13, 30]), hidden behind more intense confounding component signals in the short-wave NIR, the relation of the discussed approaches to actual glucose concentration should be investigated more thoroughly, as calibration techniques (e.g., ANN) may also learn from physiological correlations, with only an indirect (unspecific) relation to glucose. These effects may drift (in intensity or due to variable lag times), or even suddenly change, but once identified it may be feasible to define situations or patients with an increased risk for inaccurate glucose measurements. The discussed methods to detect (pure) chance correlations, like randomizing reference values cannot detect such variable, but non-random physiological correlations. Without additional and validated models for the contribution of glucose related effects to the learned glucose prediction function, it is unclear if any of the presented studies is appropriate to cover cross-sensitivities and other confounding parameters, e.g., as discussed above with the evaluation of PPG signals.

Thus, we extend the discussion of physiological effects that are detectable in general by short-wave NIR measurements. Color of the skin is dominated overwhelmingly by the

hemoglobin chromophores in both redox states and melanin. With a certain blood flow, a special oxygen saturation value could be given at the capillary loops due to the arterio-venous difference, similarly also an equivalent difference for glucose exists, according to the utilization of oxygen and glucose in the neighbored tissue cells. If the blood flow changes, also the arterio-venous differences will change under the condition of constant substrate utilization, which could be an effect if for example the blood flow would be glucose concentration dependent. For the blood flow in skeletal muscle, it has been studied that an additional role of insulin is its action to increase muscle perfusion; see Ref. [65]. However, to correlate this with glucose, especially with diabetic subjects is speculative.

Based on a digital image/video, applications such as determining the spatial distribution of melanin, blood concentration, and oxygen saturation have been reported in the past, e.g., [66], with blood concentration based on the direct (DC) signal, while the alternating (AC) signal is two orders of magnitude smaller and provides information about blood pulsation that can be related to blood flow and hemodynamics. Another device of Cnoga, called TensorTip MTX, similar in hardware to the discussed glucometer, is designed to predict blood pressure from a color video stream [67]. Photoplethysmography imaging of the palm of the hand at 30 frames per second, with optics for reflection measurements, has been recently applied to detect spatial distribution of blood pulsations (amplitude and phase) [58].

For a better understanding of time and spatially resolved color measurements, we searched for literature describing the spectral color characterization of off-the-shelf digital cameras [68] and upcoming (but still uncommon) cameras optimized for surveillance applications [69]. A publication describing the step from broad spectral photometric measurements to projection into the color space dimensions is given by Petrov et al. [70], providing even a Monte Carlo simulation with a multilayered blood containing tissue model, leading to chromaticity coordinates for transmission finger measurements through and without fingernail. Such a multilayer approach may also be successful for estimating tissue integral glucose concentrations, as the computer power available nowadays allows fast modeling results.

Conclusions

The methodology and the extent of the validation studies for the presented optical non-invasive glucose monitoring techniques varies, and results for device accuracy should be taken with necessary caution as simple comparison of performance numbers, such as SEP or MARD may be inappropriate. The different methods can be distinguished with regard to technology, selectivity for glucose, and assay accuracy. Up to 1100 nm (visible and short-wave near-infrared), the technology for optical measurements, in particular by silicon-based detectors, is readily available, mobile (wearable, battery powered), and cost-efficient with high measurement speed but limitations concerning assay selectivity. Equipment for the measurement at longer wavelengths cannot currently combine all these aspects. On the other hand, selectivity for glucose is highest for signals from fundamental vibrational bands of glucose and to a lesser extent found for combination and overtone bands in the near-infrared range. The visible and short-wave regions contain evaluable and glucose-specific information, but which is rather weak and must be questioned with regard to existing cross-sensitivities, as can be seen both from spectrometric analysis and devices that require additional (non-optical) information. The safety of unspecific (indirect) methods is difficult to prove and requires large studies to show—on a purely statistical basis—a performance similar to that of minimal-invasive techniques. However, selectivity for glucose in principle does not guarantee sufficient prediction performance as requested by the medical needs and expressed, e.g., by a consensus error grid (CEG) [21, 71]. Special spectrometric modeling with estimates of glucose selectivity facilitates a time and patient-independent definition of the exploitable signal and interferences and may allow an additional and more thorough model-based risk evaluation of a method. An online detection of erroneous (and potentially dangerous) measurements is essential. Further known adverse conditions such as possible interferences from blood alcohol, infusion from mannitol, or hydroxyl-ethyl-starch solutions (as possible for intensive care patients) must be a priori excluded from glucose testing.

Key elements for non-invasive methods in general are the wavelength-dependent photon penetration depth and the selectivity for integral tissue or vascular measurements (to be precise, the heartbeat modulated vessel volume). Different penetration depths lead to the fact that tissue rich in capillaries (e.g., dermal papillae and subpapillary plexus) and low- or non-perfused sections of the skin can be probed. For the modeling of integral measurements, in most cases, the interstitial compartment has been taken into account for estimating the blood glucose concentration. For such purpose, continuous monitoring is essential, as shown by the minimally invasive CGM systems available on the market.

Non-invasive measurement devices for blood glucose have not, with a few exceptions, entered the market. There are also hurdles through the Food and Drug Administration (FDA) for the US market that a market approval after intensive clinical testing must be reached, but same applies similarly for other countries and continents. Some devices have been marketed already mainly for type 2 diabetic patients. Direct optical spectroscopic methods have always caught much attention, mostly applied for integral skin tissue measurements and being most promising. These methods have been under investigation for more than 25 years, but there is no breakthrough on the

horizon with glucose prediction errors between 1.5 and 2 mmol/l. However, for SMBG applications, even stricter guidelines have been demanded by the new ISO15179 criteria [72], which require 95% of the sensor values to be within 15% of the reference value for blood concentrations ≥ 100 mg/dl (5.6 mmol/l) or within ± 15 mg/dl for sensor values < 100 mg/dl, which includes demands also for the hypoglycemic range.

A new opportunity is provided by multiwavelength photoplethysmography, by which the arterial vasculature can be accessed as with pulse oximetry, but variations in signal amplitude and phase must be overcome to reach stable signals with an appropriate signal-to-noise ratio. Other approaches can be classified as non-direct, where a large number of calibration input data, sometimes from multiple sensors, must be provided for calibration based on machine learning techniques like ANNs that are capable for learning and modeling non-linear relationships.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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