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A Review of Optical Methods for Continuous Glucose Monitoring

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Abstract

Frequent glucose monitoring is a fundamental part of diabetes management, and good glucose control is important for long-term health outcomes. New types of electrochemical sensors that allow for continuous glucose monitoring (CGM) have become an important tool for diabetes management, although they still have drawbacks such as short lifetime and a need for frequent calibration. Other technologies are still being researched for CGM, in an attempt to replace the electrochemical sensors. Optical methods have several advantages for CGM, including potentially long sensor lifetimes and short measurement times, and many developments have been made over the last decades.

This paper will review optical measurement methods for CGM, their challenges, and the current research status. The different methods will be compared, and the future prospects for optical methods will be discussed.

Keywords: optical spectroscopy; quantitative optical methods, biomedical applications, continuous glucose monitoring, glucose sensors

Introduction

The demand for cheap and user-friendly biosensors is continually growing, and blood glucose monitoring, which is essential for diabetes management, contributes substantially to the world's

biosensor market (1). Most current glucose sensors utilise an electrochemical reaction in order to measure glucose, and these sensors have been greatly improved since their invention in the 1960's (2). However, electrochemical sensors still have some issues in terms of longevity, ease of use, and accuracy. Many companies have tried to develop and commercialise alternatives to these sensors, with limited success so far. Optical measurement methods are already widely used in both medical and industrial fields, and have several characteristics that can be advantageous for glucose sensors. Consequently, optical techniques have been of great interest in glucose sensor development.

The three market leaders that provide continuous glucose monitoring (CGM) devices today are Medtronic, Dexcom, and Abbott (3–6). The devices from these companies allow for continuous tracking of glucose levels, with measurements provided every 1-5 minutes. A small filament is placed subcutaneously, and glucose measurements are performed based on an enzymatic reaction. These CGM devices have to be replaced regularly due to the degradation of reagents and the immune response of the body (7–9). The sensors with the longest lifetimes are operational for approximately one week, and most of the devices need to be calibrated several times per day against finger-prick measurements. Both the short lifetime and the frequent calibrations increase the burden of use for patients.

Many earlier reviews of alternative glucose sensors have focussed on non-invasive glucose monitoring as the solution to current challenges with continuous glucose monitoring (10–12). However, the non-invasive CGM devices developed over the last decades have not attained any large-scale market, although several of them have been released commercially. The most prominent ones, the GlucoWatch and the Pendra, were based on reverse iontophoresis and impedance spectroscopy, respectively (13, 14). Both devices were found to be less accurate than what was portrayed in clinical trials, and the GlucoWatch caused skin irritation on the measurement site due to the electrical stimulation (15–17). The devices were discontinued not long after release, likely due to a combination of low accuracy, patient dissatisfaction, and high cost.

This review will focus on methods that employ optical measurement methods for glucose monitoring, as these technologies have many advantages for CGM. Monitoring with optical methods is reagent-free and measurements can potentially be performed in less than a minute. Cheap and miniaturised optical components have become available, which is a benefit for personalised sensor systems. Research into both invasive and non-invasive methods will be presented. Six different technologies will be described, together with the major challenges and the current research status. A discussion of optical measurement methods and a future outlook for these technologies are also included.

Continuous Monitoring of Glucose

Continuous glucose monitoring has developed as its own field over the last decades, and some background information is needed to compare different optical techniques. A short introduction to diabetes management is given below. The methods used to assess glucose monitoring devices will be also be presented, together with an overview of the different measurement sites used for CGM. Electrochemical glucose sensors will be briefly described.

Glucose concentrations are typically given in units of mg/dl or mmol/l (also written mM). Medical studies usually use mmol/l, while technical papers tend towards using mg/dl. This paper will report glucose concentrations in mg/dl, and if the referenced article uses mmol/l this number will be given in parentheses.

Management of Type 1 Diabetes

In people with diabetes mellitus type 1 (DM1) an autoimmune process has destroyed the insulin-producing beta cells in the pancreas. This makes patients with DM1 dependent on exogenous supplies of insulin to control their glucose level. Insulin can be delivered by multiple daily subcutaneous insulin injections, or by continuous subcutaneous (SC) delivery of insulin with an insulin pump controlled by the patient (18). Insulin doses are adjusted according to physical activity, meal size and composition, and the actual glucose level. Despite all efforts, most DM1 patients struggle to regulate their blood glucose level (BGL) in the desired range, and glucose can easily depart outside of the normal physiological range, typically defined as 72-180 mg/dl (4-10 mmol/l) (19, 20). Hypoglycaemia occurs when the BGL is too low (<70 mg/dl or 3.9 mmol/l), and can lead to seizures, loss of consciousness, and even death (21). Hyperglycaemia occurs when the BGL is higher than 180 mg/dl (10 mmol/l), and can lead to serious long-term complications, including kidney damage, diabetic retinopathy, heart disease and neuropathy (22).

Given the importance of keeping glucose in the desired range, management of DM1 includes frequent measurements of the BGL. Good control of the BGL reduces development of long-term complications (23, 24). Finger-prick measurements of capillary blood glucose is still the most prevalent form of daily self-monitoring of blood glucose (SMBG) in DM1 patients. These measurements are performed by pricking the skin with a lancet, and placing a drop of blood on a disposable test strip. A meter is used to measure the test strip and calculate the glucose level. Diabetic patients are recommended to measure their glucose values at least four times per day, and more often if they are at risk for large excursions from their target glucose level (25). However, SMBG by finger-prick measurements is inconvenient and painful, and many diabetic patients measure less frequently. Some even avoid glucose measurements for days or weeks. Another disadvantage of these measurements is that they only provide information about the BGL at a single

point in time. Large excursions in the BGL during the day may be missed, no information on BGL trends is available, and there is a complete lack of information at night. Hence, much effort has been invested into making CGM devices. CGM devices are sensor systems that continually provide glucose measurements for patients. Several of these devices are commercially available, and researchers are still trying to develop more precise and robust methods for CGM. CGM has been shown to improve glucose control in patients with DM1 as compared to SMBG with finger-prick measurements, especially in patients with otherwise poorly controlled glucose levels (26, 27). In addition, CGM is a prerequisite for making fully automated delivery of insulin in patients with DM1, also known as a closed-loop system or an artificial pancreas (28).

Assessing Glucose Monitoring

The precision of CGM devices is often measured by mean or median average relative difference (ARD), with most of the current commercial devices achieving median ARDs of 10-15 % and mean ARDs of 15-20%. ARD is sometimes known as absolute relative error (ARE). The ARD for each measurement is calculated as follows:

$$ARD_i = 100\% \times \frac{|Y_i - y_i|}{Y_i}$$

where Y_i is the reference glucose value and y_i is the measured glucose value. The mean and median ARDs are then calculated based on the individual ARDs. The reference glucose measurement is a measurement of the BGL performed at the same time, typically done either with a blood-gas analyser or another glucose monitoring device. ARDs are easy to calculate and interpret, but they do not indicate the direction of the error and ARDs are usually lower if a smaller glucose range is investigated.

Other common methods for evaluating glucose sensors are the Clarke error grid (CEG) and the Parkes error grid (also called the consensus error grid), shown in Fig. 1 (29, 30). The CEG plots the results from a glucose meter against a reference measurement method, and the plot is divided into five clinically relevant areas. Zone A contains the values that are within an ARD of 20% of the reference measurements, while zone B contains measurements with more than 20% error that would still lead to correct treatment. Zone C and D contain measurements that would lead to unnecessary treatment or a dangerous lack of treatment, respectively. Measurements in Zone E will indicate that the patient is in hypoglycaemia when they in reality are hyperglycaemic, and vice versa. The Parkes error grid uses the same regions as the CEG with similar definitions and improves upon some issues with the CEG, such as the discontinuous transitions between some regions (e.g. direct transitions between zone B and zone E for some glucose values). **[Fig. 1 near here]**

Glucose measurements from a sensor that is under testing can also be compared to a reference method with Bland-Altman plots (31). Other standard statistical measures are frequently reported, especially in studies that are more preliminary. These include for example R, R^2, standard error of prediction (SEP), and root-mean-square error of prediction (RMSEP). This large variety of reported evaluation methods can make it challenging to compare different systems and technologies.

There has been an ongoing discussion about the best methods for quantifying the accuracy of CGM devices. For example, the CEG does not evaluate how CGM systems handle the rate of glucose change, and the continuous glucose-error grid analysis (CG-EGA) was developed in order to improve the evaluation of continuous glucose sensors (32). However, obtaining enough data for the CG-EGA is very time-consuming, and it has not been shown to be better than the CEG (33).

Measurement Sites

Many different measurement sites have been suggested for continuous glucose monitoring systems. The measurement sites can be divided into general categories based on how invasive the measurements sites are to the patients. Non-invasive methods use measurement sites where no instruments are inserted into the body. Measurements of easily available body fluids are non-invasive, and optical measurements of skin are considered non-invasive although light is sent into the body. On the other hand, sensor systems that penetrate blood vessels or the abdominal cavity are considered invasive. Methods that introduce sensor parts subcutaneously are often called "minimally invasive", as no blood vessels are compromised.

Non-invasive CGM systems have been pursued for several decades, with the goals of improving the comfort and convenience of diabetic patients who have to monitor their glucose levels daily. Measurements in sweat (34), saliva (35), and breath (36) have all been investigated, but the concentration of glucose or other correlating analytes have generally been too low, have not correlated well with the BGL, or have had too slow dynamics. Measuring in tear fluid has also been suggested, where a sensor similar to a contact lens would have to be worn on the eye for continuous measurements. However, the glucose concentration is much lower in tear fluid than in blood, and the glucose levels in tear fluid and blood do not seem to correlate well throughout the day (37, 38). Systems that measure through skin have therefore received the most attention among the different non-invasive modalities. Many technologies have been investigated, including impedance spectroscopy, ultrasound, reverse iontophoresis, as well as many optical methods (12). Light penetrates from several micrometres to several millimetres into skin depending on wavelength, and can also be used to measure in the aqueous humour of the eye. Optical methods have therefore

received a lot of attention for non-invasive CGM, and some of this research will be described below.

Minimally invasive glucose measurements are typically performed by placing sensor parts subcutaneously. The glucose measurements are then done in the interstitial fluid (ISF), which is the fluid between tissue cells, rather than in the blood. In the steady state, i.e. when blood glucose is stable, the glucose concentration in the ISF is quite similar to the BGL. However, glucose has to diffuse from blood capillaries into the ISF, which causes a time delay in ISF glucose measurements of approximately 5-10 minutes (39, 40). The commonly used electrochemical CGM systems, as mentioned, measure glucose concentration subcutaneously. Optical measurement methods can also be used to measure the ISF, with optical fibres and/or other sensor parts placed subcutaneously.

Recent research suggests that glucose measurements and insulin infusions directly in the peritoneum (abdominal cavity) will give better dynamics for controlling glucose levels (41, 42). Hence, investigations of sensing in peritoneal fluid may be an interesting avenue for CGM. The CGM system could either be implantable or have the light source placed outside the body, which would require a permanent port or fibre penetrating the abdominal wall to the measurement site. There are challenges with both approaches. An implantable sensor would have to be robust and durable without maintenance for a long time. An open port increases the danger of infection and may cause discomfort for the user. The technological challenges for a port solution will be limited, as similar port technology already exists for insulin administration (43). No matter which method is used, sensing in the peritoneum will definitely be considered invasive. To our knowledge, no CGM devices intended for peritoneal measurements have been developed yet, although some existing devices have been modified and tested in animal models (44).

Electrochemical CGM Systems

Devices using an SC sensor and the glucose-oxidase reaction are the most common CGM systems used for daily management of diabetes. The sensors have a thin filament embedded subcutaneously, which measures the glucose concentration. A transmitter is attached to the sensor and transfers data to a device used for information display. A smartphone or an included receiver shows real-time data from the sensor, often with trend arrows and alerts for hypo- and hyperglycaemia.

These sensors measure the glucose concentration via an electrochemical reaction (2). In the basic reaction, glucose-oxidase facilitates the redox reaction of glucose with water, which produces gluconolactone and hydrogen peroxide (glucose + O_2 -> gluconolactone + H_2O_2). A small electrical current amplifies the dissociation of hydrogen peroxide, which produces free electrons. The glucose concentration in the immediate area is then determined from the electrical current resulting from

these electrons. Mediator molecules other than oxygen can be used as electron donors in order to decrease the dependency on oxygen (45).

Due to the degradation of chemical reagents and biofouling the sensors have to be replaced approximately once per week, depending on the manufacturer. The user can insert the device without the help of medical personnel. The sensors also require a warm-up period after insertion, where the glucose measurements are inaccurate for up to several hours, depending on the model. This is possibly due to local trauma in the immediate area, which is caused by the sensor insertion. In addition, regular injection of an SC foreign body may induce local SC fibroses or other tissue changes over time (46). Most devices require calibrations twice per day, where the sensor is calibrated against finger-prick measurements. If the calibration process is done while glucose levels are rapidly changing, the measured glucose level on the device will not correlate well with the actual BGL. The sensor measures the glucose concentration in the ISF rather than measuring blood glucose directly, with the associated time delay as compared to the BGL. Additional delay is introduced because of the reaction process, and because glucose must diffuse to the sensor filament as the surrounding area becomes depleted (47). Consequently, alarms about low glucose levels can occur after the patient has already started experiencing hypoglycaemia, where a prompt reaction is often needed. However, many CGM systems use advanced algorithms to predict hypoglycaemia, and can reduce the perceived time delay.

Despite several limitations, these devices generally measure glucose concentrations quite well. Electrochemical CGM has become well established among physicians and patients, and has been shown to improve glucose control in patients. Any new inventions that seek to replace today's CGMs will likely have to significantly improve upon either reliability, sensitivity, specificity, sensor lifetime, or perceived quality of life in order to succeed.

Optical Methods for Glucose Measurements

Six main optical technologies are included in this review. Near-infrared, mid-infrared, Raman, and photoacoustic spectroscopy are spectroscopic, meaning that they use the direct interaction between light and glucose to determine the glucose concentration. Systems using fluorescence spectroscopy do not measure glucose directly; rather, they typically measure the signal from molecules that can reversibly bind to glucose. The last technology, optical coherence tomography, measures the change in scattering properties in tissue as a function of glucose concentration. The following sections will give an overview of how these technologies are used in glucose sensing. A brief description of the technical aspects will be provided for each method, together with a discussion on challenges and a review of the research status in the area. The examples of in vivo research are limited to more recent and well-documented systems, with a focus on systems that are intended for personal use.

The research stage and other relevant characteristics of most of these systems are summarised in Table 1. **[Table 1 near here]**

Other optical techniques, such as measuring optical rotation (48), have been suggested for glucose monitoring. However, the studies on these methods are sparse and often several decades old. There are also studies that use variants of optical techniques, such as several recent studies using photothermal deflection spectroscopy (49, 50). As these methods have mostly been investigated by single research groups it is difficult to review how well they measure glucose. The review will therefore be limited to the above-mentioned six technologies for conciseness.

Near-Infrared (NIR) Spectroscopy

The near-infrared region extends from 700 to 2500 nm and contains absorption bands primarily caused by hydrogen vibrations (CH, NH, OH). The short wave band (780-1500 nm) is used for non-invasive measurements, while for aqueous measurements the first overtone (1500-1800 nm) and the combination band (2050-2100 nm) are mostly used (51). The absorption bands are broad and easily influenced by hydrogen bonding, temperature effects and molecules with similar absorption spectra. NIR sources and detectors are readily available and cheap. Common sources are LED arrays for non-invasive studies and tungsten-halogen lamps for benchtop measurements. Doped InGaAs detectors are common, and cooled InSb detectors are also used.

In general, transmission spectroscopy is commonly used for aqueous solutions, while reflectance spectroscopy is used for non-invasive measurements. The optimal path length through aqueous glucose samples in transmission mode is dependent on the wavelength and instrumentation, and is in the range 0.5-5 mm (52). The effective path length for non-invasive reflectance measurements is dependent on penetration depth and is heavily weighted towards the upper layer of the skin. It has been estimated to 0.4 to 10 mm, depending on the wavelength (53–55).

Challenges

Sensor placement is a great challenge for non-invasive measurements. The focus has mostly been on the skin (finger-tip, forearm (56), upper-arm), but the eye (57), lip (58), tongue (59), and mouth have also been suggested. Changes in the local environment such as a sunburn, fever, sweating, swelling, or areas with scarring, tattoos or moles can interfere with the spectra, making the results hard to reproduce in different physiological states and especially between patients. Zhang et al. further discuss this issue for spectral data obtained by non-invasive measurements through the skin (60). Although the results of calibration models look promising, there is a need for more validation and variations over humidity, pressure, skin type, age, and other factors.

For invasive measurements in the ISF or the peritoneum, the water absorption is very high around 1400 and 1900 nm, resulting in a weak signal and low signal-to-noise ratio (SNR). Invasive measurements would also require a sensor structure that does not trigger immune responses and does not cause discomfort to the user, which rules out materials such as uncoated glass (61).

Molecules with absorption spectra that are similar to glucose can cause interference in NIRS measurements. Examples of known molecules with absorbance similar to glucose in the NIR range are lactate, urea (62), and sugars such as fructose. Other molecules with similar spectra are glutamine, ammonia, and glutamate (63). Interfering molecules represent a challenge for NIR sensing if not included in the initial model, as the peaks are broad, overlapping, and the glucose signal is relatively weak compared to the water absorption bands.

Research Status

Several groups have researched in vitro transmission NIRS glucose measurements in plasma (64–66), whole blood (67), and other matrices designed to simulate bodily fluids (68). Depending on the complexity of the matrix, the equipment, the concentration range investigated (typically 18-540 mg/dl), and the pre-processing methods (see (69) for a review of techniques), the RMSEP is typically in the range 9 to 45 mg/dl. For example, glucose in the presence of urea and sodium D-lactate has been reliably measured in the physiological range by Goodarzi et al. down to 36 mg/dl (2 mM) with an RMSEP down to 10.1 mg/dl (0.56 mM) (70).

An application of NIR spectroscopy for non-invasive glucose sensing was patented by Rosenthal et al. in 1992 and spurred intensive research within this area in the 90’s (71). Most of the focus within NIRS sensing has been directed at non-invasive efforts, but advances past initial trials have yet to be presented to the public. Arnold and Small have pointed out several parameters that must be investigated in non-invasive sensing for comparability with other studies: spectral range, degrees of freedom, path length, spectral variance and chemical basis of selectivity (54). Many studies do not consider these parameters, making it difficult for the reader to assess whether the correlation is due to glucose, some co-varying factor, or overfitting by the multivariate calibration model. A study considering this was performed by Olesberg et al., who measured glucose non-invasively on a skin fold on the back of one rat for approximately 7 hours (72). The glucose level was increased to above 540 mg/dl (30 mM) and held there for 2 hours, when it was allowed to return to normal. They used a fibre probe and found a SEP of 66.6 mg/dl (3.7 mM), which was improved to 35.6 mg/dl (1.98 mM) when accounting for the time delay (15 minutes). Only one animal was used, and the between-subject variation can therefore not be evaluated.

Maruo et al. demonstrated a non-invasive NIRS-based sensor with a SEP of less than 32.2 mg/dl in 2003 (56). One diabetic and five healthy human subjects were included in this study, and

the BGL was varied between 50 and 350 mg/dl. In 2006 they followed up with a clinical study with five healthy and seven diabetic subjects, where glucose varied between 50 and 500 mg/dl, and they obtained a SEP of 27.2 mg/dl (73). After this, they have been working on data analysis and perturbations to the model to account for fat content. In 2015, they published a paper detailing how a non-invasive model can be built based on Beer-Lambert's law, without the use of chemometrics (74).

The authors are not aware of any current non-invasive CGMs for DM1 on the international market, although several companies have tried to develop non-invasive NIR-based sensors since the late 90's, such as Diasensor (Biocontrol Technology), SugarTrac (Lifetrac), and Dream Beam (Futrex Medical Instrumentation). This stands as a testament to the complexity of the problem.

A less traditional approach to aqueous glucose sensing was proposed by Ryckeboer et al., who suggested measuring glucose by waveguide-based absorption spectroscopy on a silicon chip in the range 1540-1610 nm (75). The results in vitro with glucose in range 18-684 mg/dl (1-36 mM) were promising, with an RMSEP of 20.5 mg/dl (1.14 mM). There have been no clinical trials, but a patent suggesting that the sensor can be miniaturised and implanted was granted in 2017 (76).

A minimally invasive chip-based NIR CGM sensor using microdialysis of ISF has been suggested by Mohammadi et al. The sensor has been used in two in vivo trials, the first on 10 DM1 patients for 30 hours (77), and the second one with six subjects for 12 hours (78). The glucose concentration range was approximately 60-350 mg/dl. The measurement accuracy was 13.8% overall mean ARE in the first study, and a mean ARD of 8.5% was obtained in the second study. The device offers an improvement over the electrochemical CGMs in that there are no degradable enzymes and thus the device can be replaced less frequently. However, it suffers from the aforementioned time lag in the ISF as compared to the BGL. The authors also reported issues with air bubbles forming in the sensor.

Some groups have combined different technologies for improved glucose prediction. Most notable within NIR technology is the research from the team around Caduff and Zanon (affiliated with Biovotin AG), who have worked towards a non-invasive wearable multisensory system based on dielectric spectroscopy (DS), temperature, humidity, and sweat sensors combined with 3 NIR LEDs. In their latest study, the sensor was used by 20 DM1 subjects with BGL in the range 30-400 mg/dl, and a mean ARD of 35.4 % was obtained (79, 80). As the authors point out, they have some challenges to overcome before the sensor matches the accuracy of CGMs on the market today. They do not suggest to improve or add to the sensors, but rather to focus further efforts on development of more complex algorithms.

Mid-Infrared (MIR) Spectroscopy

Mid-infrared (MIR) spectroscopy uses light approximately in the 4000-400 cm^{-1} (2.5-25 µm) range, although many applications focus on the 4000-1000 cm^{-1} (2.5-10 µm) range (81). Wavenumbers (cm^{-1}) are commonly used in the literature on mid-infrared spectroscopy, and will also mainly be used in this article. Glucose has absorption peaks in several areas in the mid-infrared range, most notably around 3000 cm^{-1}, around 1400 cm^{-1}, and in the 1200-1000 cm^{-1} range. Glucose absorbance in the 1200-1000 cm^{-1} range has received the most attention for sensor studies, as the features around 3000 cm^{-1} and 1400 cm^{-1} overlap with strong water absorption peaks. This absorbance is related to the skeletal vibrations of glucose, i.e. vibrations that are characteristic for the entire molecule.

Fourier transform infrared (FTIR) spectrometers are commonly used for benchtop infrared spectroscopy. These spectrometers use radiation from infrared sources such as heated silicon carbide elements, which cover the entire wavelength range. However, current FTIR spectrometers are too large for personalised CGM devices, and the total light emitted is too weak for clinical measurements. Few other radiation sources have existed in the MIR, and one of the biggest limitations for MIR spectroscopy has therefore been the lack of high-energy sources. New avenues have opened for MIR spectroscopy with the invention and development of quantum cascade lasers (QCLs) (82, 83). A QCL is a type of semiconductor laser that can be tailored to specific single wavelengths, or it can be tuneable over a desired wavelength range. Several detector types can be used in the MIR range, including thermopile, pyroelectric, and photoconductive detectors.

Most available research relies on transmission MIR spectroscopy for subcutaneous glucose measurements, or reflectance spectroscopy for non-invasive measurements. CGM systems can also use attenuated total reflectance (ATR) spectroscopy, as illustrated in Fig. 2 (84). In ATR spectroscopy, light is guided by total internal reflection (TIR) in a crystal or fibre that is in contact with the sample, and the evanescent field from the light extends into the sample. The light is detected after exiting the crystal, and the absorbance spectrum is based on the evanescent light absorbed by the sample. **[Fig. 2 near here]**

One advantage that MIR spectroscopy may have over near-infrared spectroscopy is that absorption in the MIR range is defined by fundamental molecular vibrations. NIR absorption bands are typically overtones and combination bands, which are often weaker and broader. Consequently, MIR absorption bands are relatively sharp, more selective, and have a stronger signal compared to NIR absorption bands.

Challenges

Mid-infrared light penetrates only a few micrometres into skin, and MIR spectroscopy has therefore received little attention for non-invasive glucose measurements. The MIR spectrum of skin is also

highly dependent on the skin water content, which acts as a major confounding factor. Any measurements through skin would therefore have to be calibrated individually due to individual differences in skin properties.

These challenges are minimised if MIR spectroscopy is used for measurements in the ISF or in peritoneal fluid. The largest limitation for MIR spectroscopy today is the prohibitive price of MIR lasers and other components. Tuneable lasers are necessary if a large wavelength range needs to be investigated, and these lasers have so far been limited to research use due to high price and low production volume.

Water absorption is very strong in the MIR spectrum, and much stronger than glucose absorption, which means that a high SNR is needed for accurate measurements.

Research Status

MIR spectroscopy has been used to measure glucose accurately in different artificial solutions and in vitro bodily fluids. Several early studies were reported in the 90's by the Heise group, using FTIR spectrometers for the measurements (85, 86). Although both the data analysis and spectrometers have improved since then, these studies demonstrated that glucose concentrations could be predicted with adequate accuracy at physiological concentrations (RMSEP = 10.4 mg/dl). Glucose has also been measured with high accuracy in different aqueous solutions and in vitro fluids using QCLs. Brandstetter et al. reported a study which included in vitro human serum samples, and were able to measure glucose concentrations with an RMSEP of 6.9 mg/dl, where the glucose concentration range was approximately 20-140 mg/dl (87). Broad wavelength ranges have typically been investigated in these studies, with multivariate data analysis being used to extract the relevant information. This would necessitate the use of tuneable MIR lasers if the same principle is used in CGM sensors, and these lasers are currently too large and expensive for personal use. However, sufficiently accurate concentration predictions may also be performed with only a few wavelengths or a narrow wavelength range, which could be handled with smaller lasers (88, 89).

Several research groups have studied MIR spectroscopy for CGM. The Gmachl group performed non-invasive measurements of the back-scattered light from the skin between the thumb and forefinger (90). Measurements were performed in three human subjects, with 84% of the measured glucose values in zone A of the CEG. Glucose was measured in the range 75-160 mg/dl, and the accuracy of the system is therefore unknown for the hypoglycaemic and hyperglycaemic ranges. The group is now using an integrating sphere in the set-up in order to collect more light and improve signal stability (91).

Vrančić et al. developed a system using a QCL at a single wavelength (9.7 μm), and tested the system with transmission mode SC measurements in 3 rats (92, 93). They were able to measure

with integration times down to 4 seconds, resulting in practically continuous measurements. The CGM measurements followed the reference measurements closely, and gave a median ARD of 11.0%. The measured glucose range was approximately 80-550 mg/dl. These measurements were performed for approximately 3 hours in each rat, and over a longer time period the one-laser set-up would likely suffer from signal drift. Drift could be ameliorated by either adding a laser at a different wavelength as a reference or using a tuneable laser, as commented by the authors.

Kino et al. have reported measurements of human lip mucosa with ATR-based sensing (94). They employed an FTIR source, hollow-core optical fibres for light transport, and a multi-reflection ATR prism to perform glucose measurements around 1100 cm^{-1}. They accomplished measurement errors of less than 20%. However, they did not measure hyperglycaemic or hypoglycaemic glucose concentrations, which limits the applicability of the results. This group has also reported early results using a single-wavelength QCL source at 9.7 μm (95).

Glucose monitoring devices using MIR spectroscopy that could be used in a critical care setting have been developed. The Optiscanner (96, 97) from Optiscan Biomedical has received the CE mark. In this system, blood samples are obtained via an intravenous connection to the patient, and glucose is measured in plasma after blood sample centrifugation. A spectrometer in the Optiscanner uses 25 fixed wavelengths to determine the glucose concentration. A prototype system with a QCL source has also been suggested by the Lendl group (98).

Raman Spectroscopy

Raman spectroscopy employs Raman scattering in order to observe vibrational modes in molecules (81). Raman scattering is an inelastic scattering process where a small amount of energy is transferred between a molecule and a photon. As the scattering process couples to vibrational modes in the molecule, the energy of the scattered photon is shifted by the energy of one vibrational state. The emitted photon can have lower or higher energy than the absorbed photon, as shown in Fig. 3. Raman scattering has a much smaller scattering cross section than elastic scattering, and standard Raman spectroscopy usually requires long acquisition times. **[Fig. 3 near here]**

The resulting frequency shift is particular to the vibrational modes of the molecule and independent of excitation photon frequency, and therefore the Raman spectrum for glucose can be quite clearly distinguished from other biological compounds. A single-wavelength source is sufficient to produce the entire Raman spectrum, as only the frequency shift is measured. The use of visible or NIR light gives the advantage of employing widely available optical components.

The Raman signal can be increased by several orders of magnitude with the use of surface-enhanced Raman scattering (SERS) (99). In SERS the electromagnetic field is highly amplified in the presence of metal nanoparticles, because of local surface plasmon resonances. This is usually

realised by incorporating a SERS substrate in the sensor system, which is covered by metal nanoparticles or a roughened metal surface. When using SERS one has to consider fabrication process, biocompatibility and the stability of the metal nanoparticles.

Challenges

Raman spectroscopy uses visible or NIR wavelengths for excitation, which can induce a background fluorescence signal. This can be minimised by using longer wavelengths, where biological compounds are typically less fluorescent. The application of visible or NIR light reduces the absorption by water, which allows for measurements of aqueous samples.

The main challenge of Raman spectroscopy is the small scattering cross section, which can be 10 orders of magnitude smaller than the fluorescence cross section. This may result in the Raman scattering signal being masked by interfering fluorescence signals (100). Additionally, long acquisition times are necessary in order to obtain good a SNR.

Using SERS will improve the Raman signal and shorten measurement times, which is very beneficial for sensor development. However, implanted SERS substrates will experience biofouling, and may degrade over time. The development of SERS sensors is therefore dependent on the biocompatibility and potential toxicity of SERS substrates. Studies have indicated that at least some types of nanoparticles can aggregate in tissues, with detrimental effects to the organism (101, 102).

Research Status

Over the last few decades, there has been a great interest in developing a non-invasive CGM system based on Raman spectroscopy. In vitro glucose measurements have been reported in aqueous humour from rabbits and humans (103, 104). The aqueous humour is not as complex as blood, as it has fewer Raman-sensitive molecules and is less absorptive, which is an advantage for Raman spectroscopy. Although initial studies showed a correlation between blood and humour glucose levels (RMSEP of 22 mg/dl), the development of a device for personal use has not been realised.

Another approach for non-invasive glucose is to measure through skin. Research from the MIT George R. Harrison Spectroscopy Laboratory on continuous transdermal measurements has led to the development of a portable Raman system in transmission mode (105, 106). The Raman spectra of the thenar skin fold from 18 human volunteers showed good correlation with finger-prick measurements during an oral glucose tolerance test. 100% of the measurements were in the A and B zone of the CEG, with an RMSEP of 16.8 mg/dl. This system was also used by Shih et al. to measure glucose levels in a dog model (107). They achieved RMSEPs of approximately 27-36 mg/dl (1.5-2 mM) when the BGL was stable. Glucose values in the hypoglycaemic range were not measured.

A minimally invasive approach for glucose monitoring has been proposed by the Van Duyne group, based on a SERS chip implanted subcutaneously in rats (108, 109). Measurements have been demonstrated 17 days after sensor implantation, where only one calibration was performed. In their largest study, 100% of measurements from all rats were in zone A and zone B of the CEG. Moreover, the RMSEP was 13.7 mg/dL for low glucose concentrations (<80 mg/dl). An acquisition time of 2 minutes was reported. The SERS substrate must be evaluated with respect to its biocompatibility, as it is implanted under the skin.

To the best of the authors' knowledge, no commercialised CGM device based on Raman spectroscopy exists to date, although at least one company was able to CE mark a system. The US-based company C8 Medisensors developed the HG1-c, which was a non-invasive device that could provide glucose measurements every 5 minutes (110). The device had issues with accuracy, and although 92% of measurements were in the A+B zones of the CEG, only 52% of measurements were in the A zone. C8 Medisensors closed down in 2013.

Photoacoustic Spectroscopy

Photoacoustic spectroscopy measures light that is absorbed in matter via acoustic detection(111). Light is introduced into tissue, which absorbs and scatters according to the wavelength and tissue components. The absorbed energy induces local heating, which generates a sound wave through thermal expansion. The sound wave is then detected in a photoacoustic cell by a piezoelectric transducer (microphone). Photoacoustic (PA) cells are usually open-ended, and the open end is placed in contact with the sample. A simple schematic is shown in Fig. 4. **[Fig. 4 near here]**

Selective detection of glucose is achieved by using specific wavelengths that target glucose absorption bands. QCLs or FTIR sources are most commonly used for photoacoustic spectroscopy of glucose, as the MIR absorption bands are typically targeted. NIR light sources can be used if the NIR absorption bands of glucose are targeted. Acquisition times with PA spectroscopy can be as low as a few seconds, as the main limitation is the scan time of the light source.

Challenges

The challenges in PA spectroscopy for glucose monitoring are partially determined by the glucose absorption bands targeted. For MIR absorption bands it is necessary to use weak FTIR sources or expensive QCLs, while for NIR absorption bands the signal becomes much weaker.

The photoacoustic cell can be very sensitive to environmental variation, such as changes in temperature, humidity, and pressure. This has major effects on the measured glucose signal, and the accuracy seems to be limited for measurements of hypoglycaemic concentrations.

Research Status

Several groups have worked on creating a CGM device based on photoacoustic spectroscopy. The research has been focussed on non-invasive systems.

Kottmann et al. have reported the development of a small photoacoustic cell used for human in vivo measurements of glucose concentrations (112–114). Their measurements were quite accurate for glucose concentrations in the range 90-180 mg/dl ($R^2 = 0.8$). This was done using a set-up with two QCLs at fixed wavelengths, where the lasers alternated between being directed at the PA cell and a power meter. This allowed for improving issues with long-term drift. However, their best results were obtained while ventilating the PA cell with a constant flow of N_2. An N_2 flow will stabilise the humidity conditions inside the cell, but is not a feasible solution for a personalised device.

A similar sensor system based on photoacoustic spectroscopy has been reported by Pleitez et al. (115–117) They used a tuneable QCL with a range between 1220 and 1000 cm^{-1} as a source, and an open-ended PA cell was used as a cavity. Preliminary measurements were performed on volunteers who underwent oral glucose tolerance tests, and 100% of the measured glucose values were in zone A+B of the CEG.

A study of the Aprise sensor from Glucon Inc. was reported in 2007, which was a non-invasive sensor based on photoacoustic spectroscopy (118). 62 subjects were included in the study, and they underwent oral glucose tolerance, mixed meal, or glucose infusion tests. The study achieved a mean ARD of 19.9% for the sensor, and 94.6% of the paired measurements were within the A and B zones of the Clarke error grid. Although these preliminary results were quite good, the device was never commercialised. The sensor has not been described further in peer-reviewed literature, and the company website does not seem to be functional (glucon.com).

Fluorescence Sensing

Many molecules in the body are fluorescent, meaning that they can emit light at specific wavelengths after being excited by some incident radiation. Fluorescent molecules (fluorophores) can also be fabricated with specific desired properties, such as binding affinities and emission wavelengths, so that they are more useful in applications. Fluorescence sensing allows for very sensitive measurements, which has made it an interesting technology for clinical applications.

Studies have shown that glucose emits fluorescent light, and that glucose concentration affects fluorescence intensity. However, the direct fluorescent properties of glucose have not been a large focus in CGM research due to the low signal produced and issues with interfering signals. Instead, many research groups have tried to measure glucose via fluorescent labelling (119, 120). In this case, a fluorescence signal is produced from an exogenous fluorophore, i.e. a fluorophore that is

introduced into the body. These fluorophores are engineered to form a complex with glucose molecules and should only fluoresce in the presence of glucose, as illustrated in Fig. 5. The fluorescent light intensity will depend on the glucose concentration, as more fluorophores are active when there is more glucose nearby. Several fluorescent systems have been investigated for glucose sensing, including boronic acid derivatives and concanavalin A (ConA). The chosen system should have a high selectivity for glucose over similar molecules, and has to be biocompatible. **[Fig. 5 near here]**

Light in the UV or visible light range is typically used in fluorescence spectroscopy; cheap LEDs and photodiodes can therefore generally be used for measurements. These components can also be made very small, which is beneficial for wearable sensor systems. The light source that is used should not excite other endogenous fluorophores. Additionally, it is advantageous to create a fluorescent system where the fluorescence does not overlap with the fluorescence of other molecules, or with fluorescence absorption bands of other molecules, as this will be an interfering factor.

Challenges

There are several limitations for non-invasive measurements using fluorescence spectroscopy, as light scattered from skin would also be dependent on the amount of pigmentation and other differences in skin properties.

For minimally invasive and invasive measurements, fluorescence spectroscopy would still need calibration against finger-prick measurements. Drift of the fluorescence signal will occur both due to drift of the source, as well as gradual loss of fluorophores due to photobleaching.

There have been issues with achieving a linear fluorescent signal over the entire physiological range of glucose concentrations (119). Many fluorophores also bind other sugars such as galactose and fructose. Issues with saturation and the presence of interferents therefore limits the number of useful fluorophores.

Research Status

Several studies were conducted in the early 2000's into different possible fluorophores for glucose measurements, but many of these struggled with challenges such as low solubility and narrow measurement ranges. Several groups have tried to develop contact lens glucose sensors using fluorescence spectroscopy over the last decades (121–123). As mentioned, the glucose level in tear fluid does not seem to correlate well with the BGL, which has been a challenge for this research.

A subcutaneous glucose sensor based on fluorescence spectroscopy was first suggested in 1979 by Schultz et al. (124) This sensor concept has been further researched by the same group

(125, 126), and is now under development by BioTex Inc. under the name Fluorescence Affinity Sensor (FAS). This sensor utilises a fluorophore inside a hollow dialysis fibre that is connected to an optical fibre, where fluorescence-labelled ConA is used as the fluorophore. Glucose displaces the dextran bound to the ConA, which induces a fluorescent signal proportional to the glucose concentration. The sensor has been tested in several pilot studies in humans and pigs (127, 128). For the human pilot study, a mean ARE between the sensor and the reference measurement of 13% was achieved. The delay between the sensor measurement and the reference BGL was on average 4 minutes.

A clinical trial was reported by Müller et al., where they presented a similar fluorescence-based CGM system called FiberSense (129). Their measurement method was also based on labelled ConA. The sensor was implanted in two sites in six subjects for 14 days. The overall mean ARD was 8.3% for sensors used on the upper arm, and 11.4% for sensors used on the abdomen. The photometer with the source and detector was worn only during measurement sessions, while the sensor head was worn continuously for the entire study. The measurement sessions lasted for approximately 3 hours, and few data points were collected in the hypoglycaemic range. The sensor was calibrated once per day against finger-prick measurements.

The American company Senseonics has released the Eversense CGM system in Europe after receiving the CE mark in 2016. The Eversense has a mean ARD of 11.1% (130). This system consists of an implantable sensor that is placed under the skin, a removable transmitter that is worn over the sensor, and a smartphone app that receives the signal from the transmitter (131). The sensor is cylindrical with dimensions 3.3 mm x 15 mm, and can be inserted subcutaneously through a small incision. The sensor is approved for 90 days of continuous use before a replacement is necessary.

The sensor itself consists of a small polymer case. A light-emitting diode (LED) in the case excites the fluorophore and two photodiodes measure the fluorescent signal. The outside of the case is covered in a glucose-indicating hydrogel. Glucose reversibly binds to a boronic-acid derivative, which serves as the fluorescent indicator in the hydrogel.

To date, this is the only commercially available wearable CGM device that is based on an optical method. The sensor has a long lifetime relative to other commercially available glucose sensors, but must be placed through a small surgical incision in the arm by a physician. This may give some discomfort and risk of infection, although questionnaires answered by users indicate that the implantation is acceptable (132). Similar to other devices, the Eversense sensor also needs to be calibrated with finger-prick measurements twice per day.

Optical Coherence Tomography

Optical coherence tomography (OCT) is a measurement method that uses an interferometer with low coherence light (133). OCT requires one reference and one sample arm for the light, a moving window to vary the path length, and a photodetector for the signal. The light scattered back from tissue is combined with light from the reference arm, and the interference signal is sent to the photodetector. An interferogram is created if light from both arms has travelled the same optical distance, i.e. within the coherence length. The refractive index of the ISF will change as the glucose concentration changes, which in turn changes the scattering coefficient. This change in scattering coefficient and concomitant variation in the interferogram is used to determine the glucose concentration.

OCT typically employs light in the NIR range, and as in NIR spectroscopy relatively cheap and small components are available. This method is used in several applications for 3D imaging with micrometre resolution, such as imaging of biological tissues.

Challenges

OCT is sensitive to motion artefacts, as any changes to the reference or sample arm lengths will interfere with the output signal. Non-invasive OCT is also sensitive to changes in the local environment of the skin, such as variations in skin temperature, pH, and humidity.

The measured change in scattering coefficient is relatively small, which is a major challenge for OCT in glucose sensing. The scattering coefficient can be affected by variations of other physiological compounds, and corrections must be made for individual differences in skin properties.

Research Status

There has been some research on OCT for non-invasive glucose measurements.
Larin et al. reported several studies that purported to show that OCT could be used to measure blood glucose non-invasively (134, 135). In vivo measurements in their OCT system correlated quite well with the BGL ($R = 0.88$), but both motion artefacts and skin temperature could significantly affect the OCT signal.

Several other research groups have been able to attain similar results with OCT and related systems, but it has not seemed to move past preliminary in vivo studies (136, 137). The company GlucoLight apparently worked on a glucose monitoring device based on OCT, and filed several patents in the late 2000's (138, 139). A small pilot study based on this device was also published in 2008, where 12 subjects with DM1 and 15 subject with type 2 diabetes participated (140). Measurements were conducted for 2 hours in each subject, and the device achieved a mean ARD of

11.5%. Hypoglycaemic glucose concentrations were not measured, and no further results from this system have been reported.

Discussion

The development of most optical methods for glucose monitoring is still progressing quite slowly, with few systems reaching even the prototype stage. These optical methods share many of the same challenges, such as a need for miniaturisation and high price of suitable components. There is also the inherent challenge of measurements based on intensity, as such measurements are prone to signal drift. Many preliminary studies of new CGM methods also have problems with study size and duration. In vivo studies will often have results for measurements in only one or a few subjects, and for measurements performed over a few hours. This gives us some information on how a system performs under optimal conditions, but tells us very little about the between-subject variation and how the system performs for the entire lifetime of the device.

Additionally, there are separate issues for systems that attempt to measure non-invasively and invasively. The main challenges for non-invasive measurements are improving the SNR, correlation between measured glucose and the actual BGL, and the possible issues of calibrating the device to individual differences in skin properties. As mentioned, many non-invasive methods struggle with calibrating across individuals due to e.g. differences in skin water content and pigmentation. The model may work well on the person that the calibration is built on, but is often not transferable. Individual calibration can be implemented to improve device accuracy, although this is time-consuming. The main challenges for invasive measurements include minimising biofouling, extending sensor lifetime, correcting for signal drift, and ensuring patient acceptability.

Optical methods have several general advantages for CGM. Most optical techniques are generally not dependent on any reagents, which means that the lifetime can be much longer than for electrochemical sensors. This is especially important for minimally invasive and invasive measurements. Even systems based on fluorescence spectroscopy, which are dependent on fluorophores, seem to have much longer lifetimes than current electrochemical sensors. Optical sensing does not consume glucose, and the glucose concentration is therefore unchanged in the area surrounding the sensor. Non-invasive optical measurements would also have potential for pain-free CGM that affects the body minimally, given that a high measurement accuracy can be achieved. Smaller and cheaper components are continually being developed, which is an advantage for personalised devices.

The different optical technologies all have advantages and disadvantages. Interesting in vivo results have been shown using photoacoustic spectroscopy, but the sensitivity is too low for accurate measurements at physiological concentrations. Raman spectroscopy suffers from a very

low signal that can be improved using SERS, but the challenge then becomes achieving stable surface-enhancement. The SERS substrate may degrade over time in the body, which limits the device lifetime and creates a risk for biotoxicity. NIRS has been explored extensively for non-invasive CGM, but no devices have yet been successfully commercialised. There are relatively few studies on MIRS for glucose measurements, as non-invasive measurements are less feasible than for NIRS and the price of components is generally high. Studies have shown that both NIRS and MIRS can measure glucose accurately in ISF and similar fluids, and these methods have high potential for use in minimally invasive or invasive CGM systems. CGM systems that use fluorescent labelling have progressed the furthest of all the optical methods. Several devices are in a prototype stage, and the Eversense system is currently being commercialised. Glucose can be measured accurately with good fluorescence labelling, and the sensors have long lifetimes.

Of course, it is difficult to predict how the other optical methods will fare in the future, and if any of them are more likely to succeed due to technological advantages. There seems to be a trend, especially in non-invasive glucose measurements, of increased focus on developing data processing methods. This suggests that the instrumentation has reached a state where new advances only provide incremental improvements in sensitivity and that smart enough algorithms may account for the variable factors. Unless there is a large leap in technology or data processing techniques, this may be a fundamental limit for non-invasive CGM with optical methods. Indeed, with the implantable system from Eversense and many other groups working on invasive or minimally invasive systems, it seems that we might be moving away from the idea of non-invasive methods as the optimal solution. Minimally invasive sensors are already accepted by many patients in the form electrochemical CGM devices. Utilising sensing systems developed for the peritoneum is also a possibility, and may give faster sensor dynamics. This can lead to closed-loop systems that more closely mimic the functions of a healthy pancreas.

Conclusions

Current electrochemical CGM devices are an improvement for diabetes management as compared to intermittent finger-prick measurements, but they have short sensor lifetimes and must be calibrated against finger-prick measurements daily. Much effort has been spent on research into glucose measurement methods that could potentially replace these devices. Optical methods have many beneficial properties for CGM, but few devices have been commercialised despite decades of research.

Electrochemical devices are now the gold standard for CGM, and new devices will likely have to improve upon some aspects of these sensors in order to be accepted by patients and physicians. Several studies have shown progress for sensor systems based on spectroscopy, with

some of the most promising results for MIR, NIR and Raman spectroscopy. Systems based on fluorescent labelling sensors have been the most successful so far, with several prototypes in development and one system being commercialised. The Eversense is a promising alternative to current electrochemical methods; its main advantage seems to be the comparably long lifetime. As long as patients tolerate the sensor insertion and removal, it may be the first optical CGM device to enjoy success.

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List of Abbreviations

ARD – Absolute relative difference
ARE – Absolute relative error
ATR – Attenuated total reflectance
BGL – Blood glucose level
CEG – Clarke error grid
CG-EGA – Continuous glucose-error grid analysis
CGM – Continuous glucose monitoring
ConA – Concanavalin A
DM1 – Diabetes mellitus type 1
ISF – Interstitial fluid
FTIR – Fourier transform infrared
MIR – Mid-infrared
NIR – Near-infrared
OCT – Optical coherence tomography
PA - Photoacoustic
QCL – Quantum cascade laser
RMSEP – Root-mean-square error of prediction
SC – Subcutaneous
SEP – Standard error of prediction
SERS – Surface-enhanced Raman spectroscopy
SMBG – Self-monitoring of blood glucose
SNR – Signal-to-noise ratio
UV – Ultraviolet

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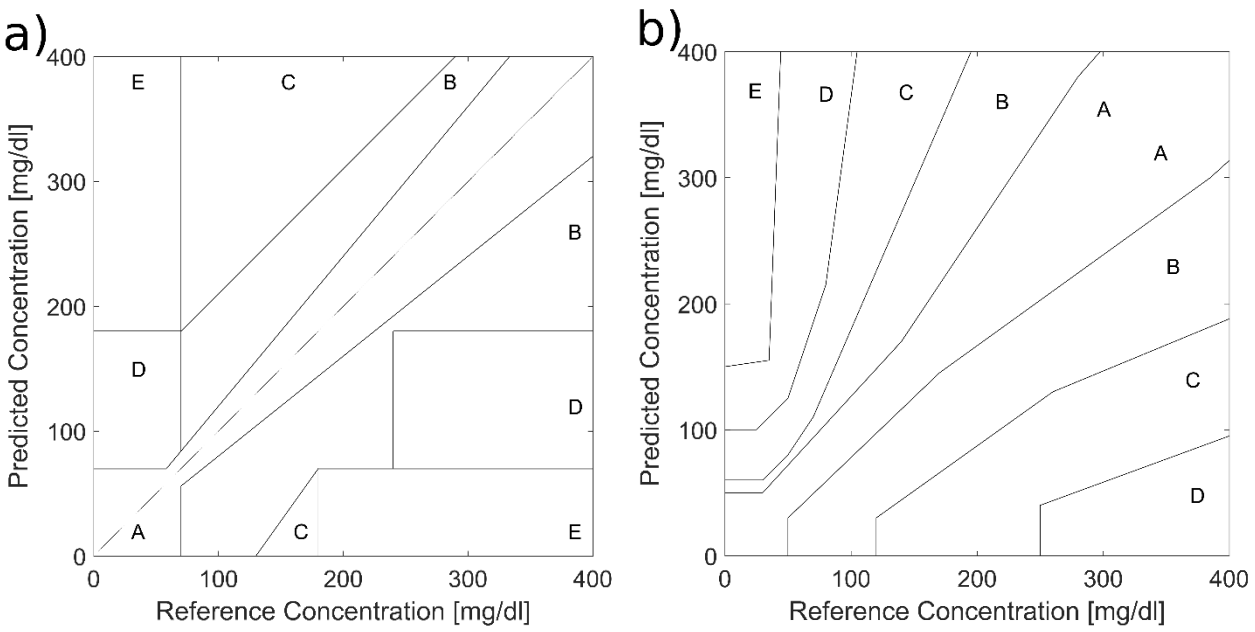

Fig. 1: a) Clarke error grid and b) Parkes error grid for glucose monitoring. The y-axis indicates glucose values measured with the new device, while reference values are represented on the x-axis. See the text for an overview of the different zones.

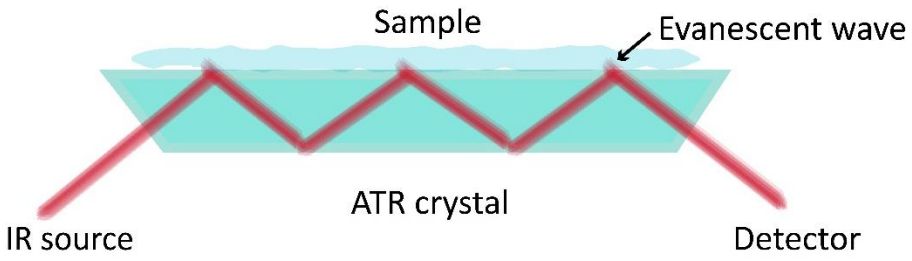

Fig. 2: Attenuated total reflectance (ATR) is a common technique in infrared spectroscopy. Light can undergo multiple internal reflections in a crystal or fibre with high refractive index. The evanescent wave resulting from this can extend into a sample that is in contact with the crystal. Absorption of this evanescent wave is used to construct an infrared absorption spectrum.

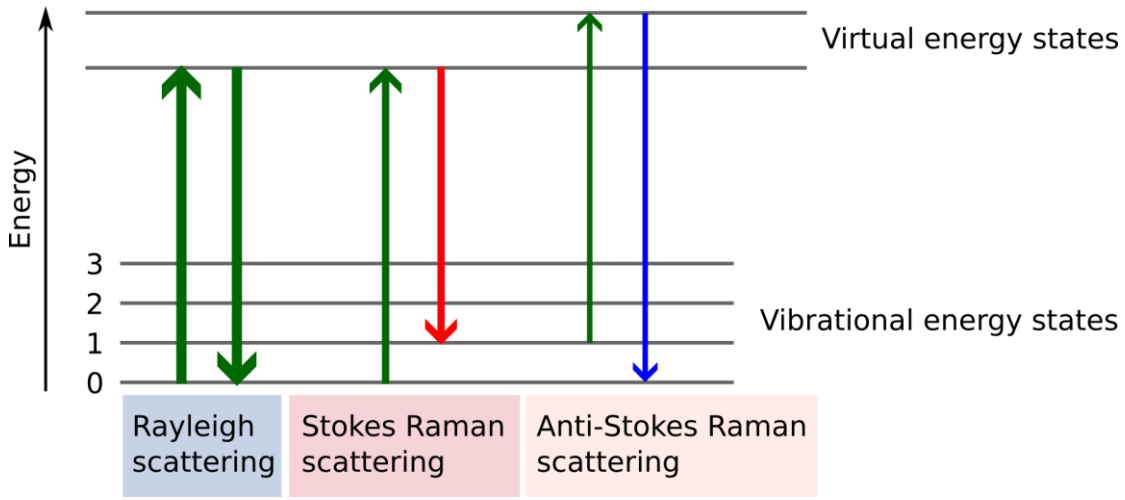

Fig. 3: Rayleigh scattering is elastic, and does not change the energy of the photon. The molecule absorbs energy in Stokes Raman scattering, where the photon is shifted to a longer wavelength, and vice versa for anti-Stokes scattering. Measurements of Raman scattering are used in Raman spectroscopy to detect and quantify molecules.

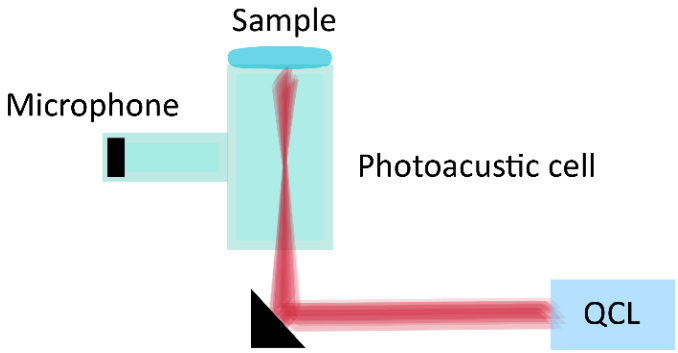

Figure 4: Schematic of a photoacoustic spectroscopy set-up. The source can be a QCL or another infrared source. A sample is illuminated and heated, and the resulting sound waves propagating in the photoacoustic cell are detected by a microphone.

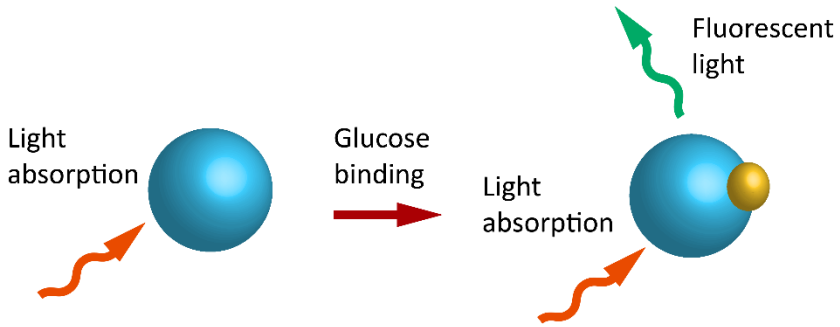

Figure 5: Sensing through fluorescent labelling. Fluorescence is suppressed when glucose is not present. When glucose binds to the fluorophore, fluorescence can occur.

Table 1 Summary of research results using optical measurement methods for glucose monitoring

Method and wavelength	**Research stage and type**	**Citations/Company**	**Measurement site/ solution**	**Glucose range**	**Accuracy**
Transmisison **near-infrared spectroscopy,** combinational band and first overtone	in vitro	Goodarzi et al. (70)	Aqueous solutions and serum solutions	36-540 mg/dl (1-30 mM)	RMSEP down to 10.1 mg/dl (0.56 mM)
Transmission **near-infrared spectroscopy,** 2-2.5 µm	in vivo, non-invasive	Olesberg et al. (72)	Skin fold, rat	90-630 mg/dl (5-35 mM)	SEP of 35.6 mg/dl (1.98 mM)
Diffuse reflectance n**ear-infrared spectroscopy,** first overtone	in vivo, non-invasive	Maruo et al. (73)	Skin, forearm	50-500	SEP of 28.7 mg/dl and 27.2 mg/dL
Transmission **near-infrared spectroscopy,** first overtone	Prototype in vitro, aimed at in vivo invasive	Ryckeboer et al. (75)	Aqueous solutions	18-684 mg/dl (1-36 mM)	RMSEP of 20.5 mg/dl (1.14 mM)
Transmission **near-infrared spectroscopy** combined with microdialysis, 1300, 1450, 1550 nm LEDs	Prototype, invasive	Mohammadi et al. (78)	Microdialysate from arm	60-350 mg/dl	Mean ARD 8.5%
Diffuse reflectance **Near-infrared LEDs** in short wave range	in vivo, non-invasive	Zanon et al., Biovotion AG (80)	Skin on the upper arm	30-400 mg/dl	Mean ARD 35.4%
ATR mid-infrared spectroscopy, FTIR source	in vitro	Heise et al. (86)	Blood plasma	36-482 mg/dl	RMSEP = 10.4 mg/dl
Transmission **mid-infrared spectroscopy**, 1230-1030 cm^{-1}	in vitro	Brandstetter et al. (87)	Blood serum	Approx. 20-140 mg/dl	RMSEP = 6.9 mg/dl
Back-scattered **mid-infrared spectroscopy**, 8-10 µm	in vivo, non-invasive	Liakat et al. (90)	Thenar skin fold of the hand	80-160 mg/dl	84% of measurements in zone A of CEG
Transmission **mid-infrared spectroscopy**, 9.7 µm	in vivo, minimally invasive	Vrančić et al. (93)	Transcutaneous, rats	Approx. 75-600 mg/dl	Median ARD 11.0%
ATR **mid-infrared spectroscopy**, 1155 cm^{-1}	in vivo, non-invasive	Kino et al. (94)	Inner lip, human	Approx. 75-175 mg/dl	Measurement errors less than 20%, R^2 = 0.75

Raman spectroscopy in reflection mode, 785 nm	in vitro	Pelletier et al. (104)	Aqueous humour of the eye, human	0-800 mg/dl	RMSEP = 22 mg/dl
Transmission **Raman spectroscopy,** 830 nm	in vivo, non-invasive	Kong et al. (106)	Thenar skin fold of the hand	75-320 mg/dl	R^2=0.81, RMSEP=16.8 mg/dl
Transmission **Raman spectroscopy**, same system as Kong et al. (106)	in vivo, non-invasive	Shih et al. (107)	Ear, dog	100-460mg/dl (5.6-25.6 mM)	RMSEP approx. 27-36 mg/dl (1.5-2 mM)
Surface-enhanced **Raman spectroscopy**, 785 nm	in vivo, minimally invasive	Ma et al. (109)	Subcutaneous, rats	31-600 mg/dl collectively from 5 rats	100% of measurements in zone A+B of CEG
Photoacoustic spectroscopy, dual-wavelength scheme around 1100 cm^{-1}	in vivo, non-invasive	Kottmann et al. (114)	Arm skin	90-170 mg/dl	R = 0.8
Photoacoustic spectroscopy, 1220-1000 cm^{-1}	in vivo, non-invasive	Pleitez et al. (116)	Arm skin	40-250 mg/dl, collectively from 3 subjects	100% of measurements in zone A+B of CEG
Fluorescence sensing	Prototype, minimally invasive	Dutt-Ballerstadt et al., Biotex Inc. (127)	Subscutaneous on arm	100-350 mg/dl	Mean ARE 13%
Fluorescence sensing	Prototype, minimally invasive	Müller et al., Eyesense GmbH (129)	Subcutaneous on arm and abdomen	60-370 mg/dl	Mean ARD 8.3% on arm, 11.4% on abdomen
Fluorescence sensing	Product, invasive	Mortellaro et al., Senseonics Inc. (131)	Implanted subcutaneously	40-400 mg/dl	Mean ARD 11.1%
Optical coherence tomography, 1300 nm	in vivo, non-invasive	Larin et al. (135)	Ear, rabbit	110-400 mg/dl	R = 0.88
Optical coherence tomography, 1310 nm	in vivo, non-invasive	Gabbay et al. GlucoLight (140)	Skin, human	98-442 mg/dl	mean ARD 11.5%