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Review

Noninvasive Electromagnetic Wave Sensing of Glucose

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Abstract: Diabetic patients need long-term and frequent glucose monitoring to assist in insulin intake. The current finger-prick devices are painful and costly which make noninvasive glucose sensors highly demanded. In this review paper, we discuss several advanced electromagnetic (EM) wave based technologies for noninvasive glucose measurement, including infrared (IR) spectroscopy, photoacoustic (PA) spectroscopy, Raman spectroscopy, fluorescence, optical coherence tomography (OCT) and microwave sensing. Development and progress of each method are discussed regarding fundamental principle, system setup and experimental results. Despite the promising achievements reported previously, there is no established product to obtain FDA approval or survive marketing test. Limitations and prospects of these techniques are discussed at the end of this review.

Keywords: noninvasive glucose measurement; IR spectroscopy; Raman spectroscopy; photoacoustic spectroscopy; microwave sensing

1. Introduction

Blood glucose level is one of the most important physiological parameters which is associated with metabolic and homeostatic mechanism in human body. Diabetes mellitus is a prolonged metabolic disorder due to the insufficient insulin production or improper cell response to insulin [1]. The diabetic population was projected to be 552 million by 2030, reported by David R. Whiting and *et al.* [2], based on the data sources for 80 countries. Diabetes imposes heavy economic burden to the patients and their families. According to American Diabetes Association, the total cost of US diabetes is $327 billion in 2017 [3]. Diabetes can be mainly classified into 3 categories: Type I, Type II and gestational diabetes [4]. The first one is usually called "juvenile diabetes" which is mainly diagnosed in children and caused by the lack of insulin produced by beta-cells [5-9]. Only 5%~10% diabetes are in this form. The second one is the most prevalent among diabetic patients accounting for more than 90% [10] which is primarily caused by unhealthy lifestyle and genes [11]. It is characterized by insulin resistance and sometimes combined with reduced insulin secretion [4, 12-14]. The last category usually occurs among pregnancies and either disappear or developed to Type II diabetes after delivery [4, 15, 16]. Long-term abnormal levels of glucose (hyperglycemia when glucose level > 200 mg/dL [17] and hypoglycemia when glucose < 70 mg/dL [18]) often lead to complications including accelerated atherosclerosis [19], stroke [20], neuropathy [21], nephropathy [22], retinopathy [23] and *et al.*. In addition, it has been reported that diabetes also significantly increases the risk of cause-specific death [20, 24, 25]. Since there is no specific remission or cure of diabetes [26], daily glycemic measures need to be carried out together with active treatments (insulin injection or bariatric surgery) to improve the lives of diabetic patients. Since 1962, Clark and Lyons proposed the electrochemical method [27], glucose oxidase (GOx) has been widely applied for glucose determination. Well established glucose meters are mainly based on electro-enzymatic reactions which require a finger-prick device to get a drop of blood (~ 1 μL) and apply it on the disposable testing strip [28, 29].

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Although the accuracy of this kind of invasive devices is proved and accepted, they are discrete, causing physical pain and infection [30, 31]. Moreover, the annual cost of testing strips is estimated to be $750 per patient [32]. Therefore, semi-invasive or minimally invasive devices are developed with the aim of replacing those finer-prick devices and achieving continuous blood glucose monitoring (CBGM). They usually measure the glucose concentration in interstitial fluid (ISF) by implanting a tiny and relatively painless subcutaneous sensor. Nevertheless, the sensitivity gradually degrades as the protein builds up on the surface of sensor and hence a frequent calibration is required [33, 34]. Great effort has been devoted to the development of truly noninvasive glucose sensors employing various emerging technologies. Among those methods, electromagnetic (EM) wave sensing has drawn much attention due to its rich interactions including absorption, scattering, transmission and *et al.* with particular compounds inside body. EM wave can be classified into radio waves, microwaves, visible/infrared (IR) light, ultraviolet, X-rays and gamma rays [35], based on different frequencies or wavelengths. In this article, we will review some recent advances in EM wave sensing, more specifically, optical methods, photoacoustic spectroscopy and microwave sensing. We will discuss on the basic working principle, present the typical experiment setup and briefly state the experimental results for each method in Section 3, followed by the challenges and outlook of noninvasive glucose sensing in Section 4.

2. Performance evaluation

To evaluate the performance of noninvasive techniques and devices, the obtained data are usually calibrated and paired with references measured by invasive blood glucose meters at the same time point. Several indicators are often adopted to quantitatively assess the performance from statistical and clinical point of view. Firstly, coefficient of correlation R can be used to show degree of relationship between two data sets. Its value always varies within ±1 where positive value indicates the same variation trend while negative one represents that they vary in opposite way. Another indicator, *R-squared* (R^2) value is known as coefficient of determination which measures goodness of linear regression. Besides, root-mean-square error (RMSE), mean absolute error (MAE) and mean absolute percentage error (MAPE) are used to evaluate the deviation of measured values compared to references. In 1986, J. M. Bland and D. G. Altman claimed that using of correlation is misleading and they suggested a new statistical approach to assess degree of agreement -- Bland-Altman plot [36, 37], as shown in Figure 1(a). It can be used to show the difference between measured values and references, where the solid black line represents for their mean difference ($\bar{d}$) and the two dotted lines are "limits of agreement" whose values are calculated as $\bar{d} \pm 1.96SD$ (SD is the standard deviation of the differences). Apart from the above mentioned statistical accuracy evaluation methods, W. L. Clarke proposed to use a scatterplot to describe clinical accuracy of glucose meters which has become the "gold standard" [38]. As shown in Figure 1(b), Clarke Error Grid (CEG) is divided into five regions where A contains values within ±20% deviation of reference, B contains predictions with error > 20% but will not lead to inappropriate treatment. Data in these two regions are regarded as clinically acceptable. On the contrary, predictions falling in region C will lead to overcorrection of normal glucose levels and D represents failure to detect abnormal glucose levels for prompt treatment. Data falling in E will result in erroneous and dangerous treatment. Measurement results in these three regions are not beneficial in patients' daily care.

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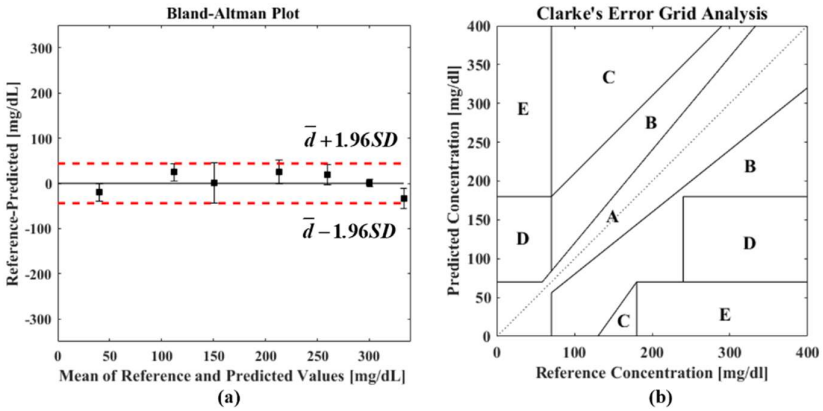

Figure 1. Examples of (**a**) Bland-Altman plot and (**b**) Clarke Error Grid Analysis.

3. Methodologies for noninvasive glucose sensing utilizing electromagnetic waves

In this section, various EM wave based noninvasive glucose monitoring techniques are reviewed in details including the basic theories, system instrument and laboratory test.

3.1. Infrared (IR) spectroscopy

There are several kinds of interactions between light and biological tissues depending on the properties of target tissues and characteristics of illuminating light source. The interactions can be mainly categorized into absorption, transmission, emission, reflection and scattering. Among those, absorbance information is by far the most widely used. Molecules with vibrational and rotational motions tend to absorb light at matched frequencies or wavelengths due to resonance. More specifically, chemical bonds can move in the form of bending, symmetrical stretching, asymmetrical stretching and *et al*. [39]. The quantum vibrational energy bands usually fall in infrared (IR) region [40]. Thus, IR spectroscopy has been widely applied in analytical chemistry for characterizing samples in various states such as gases, liquids and solids. Based on different excitation sources, it can be classified into near infrared (NIR) spectroscopy [41], mid infrared (MIR) spectroscopy [42] and far infrared (FIR) spectroscopy [43]. Herein, we will discuss more on the first two considering the specific application for noninvasive glucose measurement.

3.1.1. Near infrared (NIR) spectroscopy

The NIR radiation was discovered by Sir William Herschel in 1800 [44] and the first NIR spectra was obtained in 1881 by Abney and Festing in the range of 1000 - 1200 nm [45]. Nowadays, NIR spectroscopy utilizes the EM wave in the range of 700 - 2500 nm [41, 46-48], which covers several optical windows where photons have less interactions with interfering tissue compounds like water, hemoglobin and lipid, so that the penetration depth can achieve several millimeters [34, 49], where capillary beds locate [50-52]. The absorption in this wavelength range corresponds to combination, first, second or higher order overtones of fundamental molecule's stretching and bending [41, 53, 54]. Glucose is a kind of monosaccharides with the molecular formula $C_6H_{12}O_6$ in the form of pyranose. It has several absorption peaks in NIR region discovered previously, which are listed in Table 1.

Table 1. Absorption peaks of glucose in NIR region and corresponding functional groups

No.	Wavelength (nm)	Functional Group
1	2273	Combination of O-H/C-O stretching [54]
2	2261	νCH + νCCH [55]
3	1688	2νCH [55]
4	1638	First overtone [56]
5	1536	νOH + νCH [55]

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6	1408	2νOH [55]
7	1126	3νCH [55]
8	1042	Combination of νCH [57, 58]
9	1018	Combination of νCH [59]
10	939	3νOH [55]
11	930	$3\nu CH_2$ [57]
12	910	4νCH [57, 58]

The attenuated light simply due to analytes absorption after passing through tissue is governed by Beer-Lambert Law which is expressed as

$$I = I_0 \exp(-\mu_a l)\,, \tag{1}$$

where μ_a is absorption coefficient and l is effective optical path length. μ_a is proportional to εC cm^{-1} where ε represents for molar extinction coefficient and C is molar concentration of the analyte [55, 60, 61]. μ_a may increase with elevated glucose level due to its intrinsic absorption or decrease due to water displacement effect. The latter is less specific as changes of other components can also result in the same effect [55].

Basic instrumentation of NIR spectroscopy consists of a light source such as tungsten halogen lamp and an IR detector. Then, the analog signal is filtered and amplified before digitized by analog-to-digital converter (ADC). Given the complexity of interfering component matrices, various signal processing techniques are adopted to extract glucose-related information including principle component regression (PCR), partial least-square regression (PLSR) and artificial neural network (ANN) [62-66] based analysis.

Stephen and *et al.* reported *in vivo* detection of glucose using NIR diffuse reflectance spectroscopy on seven diabetic patients and three healthy volunteers [67]. The forearm was selected as measurement site as it's uniform and less susceptible to movement. Spectra were collected in the range of 1050 – 2450 nm and calibrated by PLSR of smoothed first derivative. Three out of seven diabetic subjects were successfully measured and oral glucose tolerance test (OGTT) on three healthy volunteers showed accurate prediction using the collected spectra. Although the results were encouraging, limited success was achieved due to system instability and sampling variation. Katsuhiko and *et al.* reported *in situ* experiment results using the similar method except that the wavelength applied is from 1300 nm to 1900 nm [68]. Moreover, two optical fibers were employed for illumination and collection to control the penetration depth by adjusting fiber separation distance. Five healthy and one diabetic subjects were tested by OGTT. Time correlation between predicted and reference glucose levels were presented and the same data sets were also evaluated by CEG analysis. 71.3% data are in Zone A, 21.3% data are in Zone B and the remaining are in Zone D. Xue and *et al.* compared linear and nonlinear regression methods by using PLS and ANN on living rats [69]. Besides, different combinations of pretreatment methods including first derivative, second derivative, vector normalization and *et al.* were also investigated. In their study, PLS achieved a better performance than ANN did with lower RMSE and higher R.

3.1.2. Mid infrared (MIR) spectroscopy

Unlike NIR spectroscopy, MIR spectroscopy employs longer wavelength ranging from 2500 – 10000 nm [70] where the well-known "fingerprint region" of glucose locates. The featured absorption peaks in this region are sharper and provide better specificity than NIR spectroscopy does. The maxima of glucose absorption in MIR region is listed in Table 2.

Table 2. Absorption peaks of glucose in MIR region and corresponding functional groups

No.	Wavelength (nm)	Functional Group

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1	8000	C-H bending vibrations [70-73]
2	8244	[74]
3	8658	Pyranose ring [75, 76]
4	8680	[77]
5	9290	C-H bending vibrations [70-74, 77]
6	9551	C-H bending vibrations [70-73]
7	9680	ν(C–O–H) or ν(C–O–C) vibration [72-74, 77, 78]
8	9746	C–O–H bending vibration [70, 72, 73]

Despite the relatively good specificity or selectivity, penetration depth is severely limited due to the strong absorption of water and lipid [79]. Thus, MIR light can only passes through the first layer of skin – stratum corneum with a thickness of 10 - 20 μm [80] and detect glucose in interstitial fluid (ISF) found in stratum spinosum layer [74, 81]. It was proved that ISF in epidermis has strong correlation with blood glucose in spite of several minutes delay [82-85]. Thanks to the recent development of Quantum Cascade laser (QCL) with high power, several groups have reported *in vivo* applications of MIR spectroscopy [76, 86-90]. Liakat and *et al.* proposed a system with external cavity QCL and a hollow core fiber to deliver light to human palm. Then, backscattered light was collected by a fiber bundle and mercury cadmium telluride (MCT) detector. PLSR and second derivative spectroscopy were applied for prediction of three human subjects. All data points fall in Region A and B of CEG which shows that maximum error of prediction results is within 20%. One hour continuous measurement was also conducted which showed general trend of glucose variation successfully. Their group recently improved the system by adding an integrating sphere to enhance collection efficiency of backscattered light [90]. Kino and *et al*. adopted attenuated total reflection (ATR) spectroscopy and utilized evanescent wave generated when total internal reflection occurs, to penetrate into the sample. The absorption of evanescent wave by the sample can be measured by MCT detector to infer glucose concentration. Their hollow optical fiber based spectroscopy system is equipped with a trapezoidal ATR prism which allows multiple reflections to enhance sensitivity [76]. Inner lip mucosa was selected as measurement site owing to the relatively thin stratum corneum and lack of keratinized layer which makes the ISF accessible to evanescent wave. They found that absorption peak at 1155 cm^{-1} was most relevant to glucose, attributed to its pyranose ring structure. *In vivo* experiment was conducted. The R^2 value of 0.75 was achieved and the all the data points were in Region A of CEG.

3.2. Photoacoustic spectroscopy

Photoacoustic (PA) effect refers to the phenomenon that object absorbs heat from light and undergoes thermal expansion followed by generation of acoustic signals. Combining the high contrast of EM wave and the deep penetration of acoustic wave in biological tissue, PA technique is able to achieve prominent performance in bio-sensing and bio-imaging applications. Although theoretically, any kind of EM wave can generate PA signal, vis/IR laser is the most frequently reported due to the wide availability of source, convenience of manipulation and rich functionality. Compared to IR spectroscopic methods for glucose detection, PA spectroscopy collects acoustic wave which is more immune to tissue scattering and directly related to laser energy deposited in skin, yielding deeper penetration and better sensitivity. Besides pure optical properties like absorption, PA signal also contains information about mechanical or acoustic properties of tissue [91, 92] which could be related to glucose concentration. The received PA signal by ultrasound transducer at position z can be expressed by one-dimensional wave equation along z-direction [93] and solved by Green's function [94] as follows:

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$$p(z,t) = \frac{\beta v^2}{2C_p} \eta F \mu_a \delta(t - \frac{z}{v}), \quad (2)$$

where β is thermal expansion coefficient, v is sound velocity and C_p is heat capacity at constant pressure. η represents for optic-heat conversion efficiency and F represents for laser fluence. Not only μ_a but also v varies with glucose concentration which can be utilized for prediction [95-97]. Similar to optical spectroscopy, laser wavelengths ranging from NIR to MIR have been adopted in various studies [74, 98-101].

Pleitez and co-workers reported *in vivo* glucose measurement in human epidermis [74]. Their system consists of external cavity QCL (1000 -1220 cm^{-1}) as illuminating source, a photoacoustic cell whose resonance frequency was designed to match the laser repetition rate. PA signal was collected by a microphone, amplified by a pre-amplifier and sent to a lock-in amplifier. OGTT was carried out and hypothenar of hand was tested. The mean prediction errors (MPE) of healthy and diabetic volunteers are 11 mg/dL and 15 mg/dL, respectively. All data points fall in critical lines of CEG. Sim and *et al.* combined the MIR PA sensor with raster scan to investigate the microscopic structure of skin and reduce the skin condition variation during measurement [100]. Index finger was in direct contact with PA cell and the resolution achieved was 90 μm. They suggested that the dark area between friction ridges of finger was non-secreting and immune to sebum and sweat where better prediction results could be achieved. The experimental setup and acquired images are shown in Figure 2.

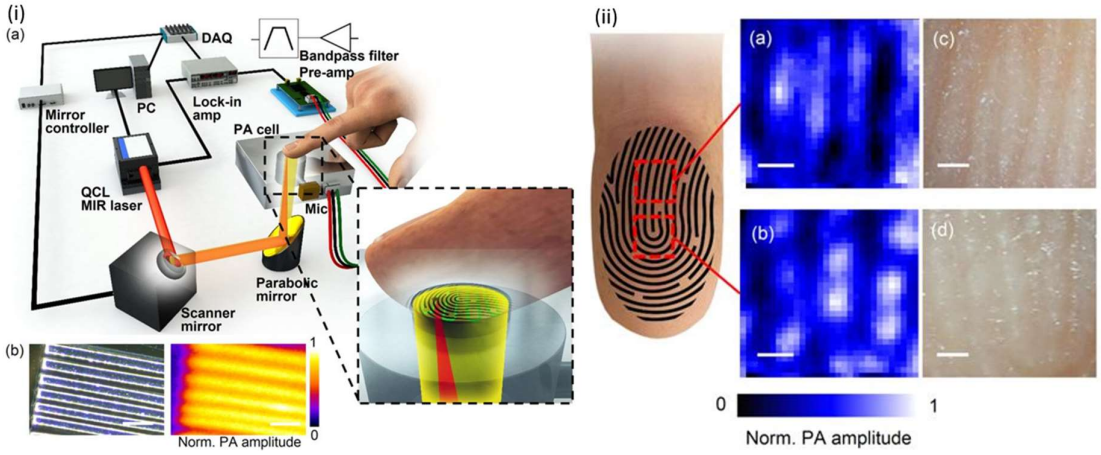

Figure 2. (i)(a) Schematic of position scanning PA microscopy system and (b) system resolution evaluation by SU-8 structure. (ii) PA images (a)(b) and corresponding micrographs (c)(d) of two fingertip regions. Reprinted with permission from [100].

Zhang and co-workers proposed to utilize both PA signal amplitude and time information to enhance prediction accuracy by data fusion, without increasing apparatus and system complexity [101]. They employed NIR laser at ~1600 nm which is one of the broad glucose absorption peaks. Glucose solution at both high and low concentrations were tested and the prediction accuracy was significantly enhanced by data fusion compared to single-parameter based prediction. The prediction results on glucose solution within physiological range (0 – 400 mg/dL) were evaluated by CEG and shown in Figure 3.

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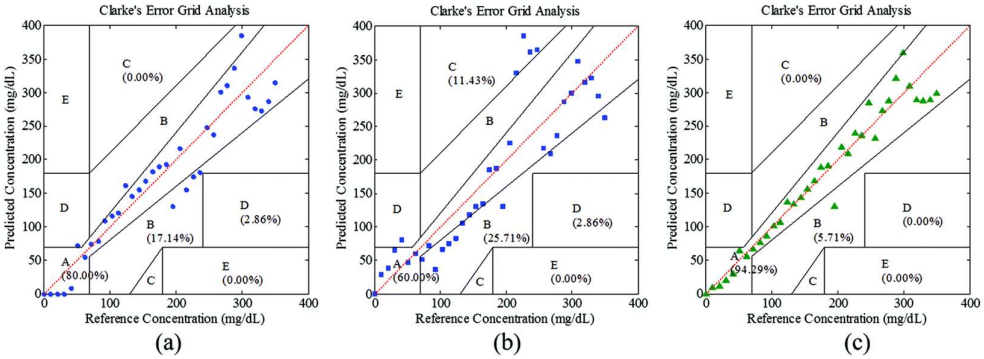

Figure 3. Correlations between references and predicted glucose concentrations shown in CEG by using (a) PA amplitude, (b) time delay and (c) data fusion. Reprinted with permission from [101].

3.3. Fluorescence spectroscopy

Fluorescence refers to the phenomenon that substances emit light (usually at longer wavelength) when absorb EM radiation. Fluorescence spectroscopy is useful in medical and biochemical analysis of chemical groups. Excitation source usually falls in ultraviolet (UV) region with high photon energy. Fluorescence has the advantage of high sensitivity which even allows for single molecule detection [102]. In addition, the characteristic emission of a certain fluorophore also guarantees high specificity. Fluorescent methods for glucose measurement can be based on intrinsic skin fluorescence spectroscopy (SFS) or specially designed molecule reporters. For design of extrinsic fluorophores, several factors including quantum yield, photostability, absorption and wavelength have to be considered [103]. Both fluorescence intensity and lifetime can be evaluated to provide sufficient information.

VeraLight, Inc. announced an SFS based product SCOUT DS which has obtained market approval in several countries. It aims to alert adults who is at risk of diabetes by deciding advanced glycosylation end products (AGEs). Evans and co-workers built a model to verify that glucose can be noninvasively measured by intrinsic fluorescence of reduced-state nicotinamide adenine dinucleotide and its phosphorylated derivative (NAD(P)H) in skin, when excited at 340 nm [104]. The autofluorescence at 400 – 500 nm was assessed. Stein and *et al.* reported "smart tattoo" which can be implanted subcutaneously and interrogate with light noninvasively [105]. The optical sensor was designed based on glucose oxidation:

$$Glucose + O_2 + H_2O \xrightarrow{GOx} Gluconic\ Acid + H_2O_2$$

It indirectly monitors the glucose caused oxygen consumption by a ratiometric readout and the detection limit achieved is 1.5 ± 0.2 mg/dL resulting from high signal-to-noise ratio. Shibata and *et al.* synthesized microbeads which provides reversible response and high sensitivity for *in vivo* continuous glucose monitoring [106]. Mice ear skin was selected as measurement site and the correlation between fluorescence intensity and blood glucose level was observed over 180 min with a short lag of 11 ± 5 min.

3.4. Raman Spectroscopy

Raman spectroscopy relies on inelastic scattering of photons named after C.V. Raman [107] to identify different molecules . There are two types of Raman scattering – stokes scattering when incident photons transfer energy to molecules and results in scattered photon with lower energy; anti-Stokes scattering which leads to increased photon energy when molecules transfer energy to incident photons, as illustrated in Figure 4(i). Raman spectroscopy system consists of a coherent and monochromatic light source, a grating to disperse the light, filters and a photodetector to obtain Raman spectra. Several advanced Raman techniques have been development such as surface enhanced Raman spectroscopy (SERS), resonance Raman spectroscopy (RRS), tip enhanced Raman

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spectroscopy (TERS) and their combinations. Glucose has characteristic scattering features in the range of 400 – 1500 cm^{-1} as shown in Figure 4(ii) [108].

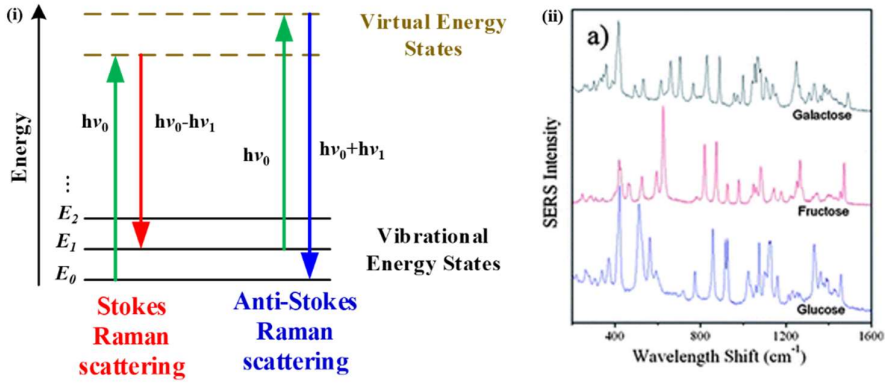

Figure 4. (i) Energy diagram of Raman scatterings. (ii) Examples of Raman spectra of different sugars. Reprinted with permission from [108].

Enejder and co-workers successfully demonstrated the first study of Raman spectroscopy for noninvasive glucose monitoring [109] on 17 volunteers. 461 spectra were collected and compared with reference glucose level. Good correlation (R^2 = 0.87) was obtained and the average prediction error is 7.7%. Kong and *et al.* developed a portable Raman spectroscopy device with efficient light collection by compound hyperbolic concentrator [110]. An 830 nm laser diode was used as excitation and another broadband source was used for diffuse reflectance. A CCD camera was employed to collect the scattering information. All the equipment was fixed on a wheel cart to achieve portability. OGTT was conducted on 18 human subjects with transmission mode. PLS and leave-one-out cross validation were applied for calibration. All of the 730 data points obtained fell in Region A and B of CEG.

3.5. Optical coherence tomography (OCT)

OCT is able to provide depth-resolved information of skin layers by detecting coherently backscattered photons. It was developed by Huang and *et al.* in 1991 [111]. The system usually consists of a two-beam interferometer and a photodiode. Envelope of interferometric signal can be used to reconstruct a cross-sectional 2D image and the light attenuation information can be calculated thereafter. Noninvasive glucose measurement by OCT is based on the fact that glucose variation in extracellular fluid (ECF) will induce refractive index mismatch change between ECF and cellular components. Thus, the scattering coefficient will change which is reflected by the backscattered signal strength.

Esenaliev and co-workers proposed an OCT sensor and tested on rabbit skin [112] for noninvasive glucose monitoring. 830 nm and 1300 nm lasers were employed in their study. They reported that the scattering coefficient decreases with increase of glucose concentration and therefore the OCT signal decreases. The signal slope was 4.5% in the range of 0 – 100 mM glucose concentration and ~1% of accuracy was obtained. Their group then did a study on human subjects in the following year [113]. 15 healthy volunteers were tested by using 1300 nm light source. The change of OCT slope was up to 2.8% with every 10 mg/dL glucose change. They pointed out that the depth-resolved OCT signal allows detection of a specific skin layer without interference from other unwanted layers. Lan and *et al.* applied OCT on diabetic patients and showed that the monitoring results were better than those on healthy subjects [114] based on *R* values (0.91 for diabetic patients and 0.78 for healthy volunteers).

3.6. Microwave sensing

Microwave refers to EM wave ranging from 1 mm to 1 m, corresponding to frequencies between 300 GHz and 300 MHz. Microwave can easily penetrate homogeneous tissue with millimeter

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thickness [115] which remains a challenge for most of the optical based methods. Besides, the cost of microwave sensors is usually low and fabrication is relatively easy. Reflection, transmission and absorption of millimeter wave are closely related to the dielectric property or relative permittivity of skin [116, 117], which varies with glucose fluctuations [118-120]. The complex permittivity varies with frequency and can be expressed by Cole-Cole equation [121]:

$$\varepsilon^*(\omega) = \varepsilon_\infty + \frac{\varepsilon_s - \varepsilon_\infty}{1 + (j\omega\tau)^{1-\alpha}}, \quad (3)$$

where ε_∞ and ε_s are dielectric constants at infinite and static frequencies and τ is relaxation time constant. These three parameters are related to glucose concentration [122]. α is a value between 0 and 1. Scattering or S parameters describing the two-port networks are usually investigated to infer glucose change. *In vitro* with tiny sensing volume (~nL) as well as *in vivo* applications utilizing microwave for glucose measurement have been studied recently [123-132] and we will mainly focus on the noninvasive detection here.

Jean and *et al.* described an open-ended spiral-shaped microstrip line contacting the thumb to monitor glucose induced permittivity variation [123]. Forward gain $|S_{21}|$ in the range of 10 MHz to 5 GHz was measured by a vector network analyzer (VNA). To ensure the stability, plastic guide and a personal soft thumb locator were added during test. PCR was adopted for calibration for 5 subjects. The strong correlation between reference and measured data can be clearly identified. Xiao and Li proposed an ultrawideband (UWB) microwave based method using a pair of planar antennas applied on earlobe [126]. A tissue mimicking phantom with fat, blood and skin layers was made to model the earlobe. Short-time Fourier Transform (STFT) was applied for time-frequency analysis. Glucose concentration from 0 to 400 mg/dL with a step size of 50 mg/dL was tested. The regularity of S_{21} parameter verified the sensor function at 6.5 GHz. Similarly, Saha and co-workers presented microstrip antennas operating at 60 GHz and measured S_{21} to predict glucose levels [131]. They demonstrated the sensor performance by *in vitro* and *in vivo* OGTT. The detection limit for aqueous glucose solution is 1.33 mmol/L (1 mmol/L = 18 mg/dL) which is far below the physiological range. Apart from amplitude of S-parameters, other characteristics of equivalent RF circuit can also be utilized to reflect permittivity change due to glucose fluctuation. Choi and *et al.* designed a split ring resonator aiming to eliminate the temperature effect for noninvasive and continuous glucose monitoring [130, 132]. The nearer ring to the measurement site is responsible to interact with tissue whereas the further ring acts as a reference resonator. The two rings are made of silver-coated copper wire which exhibit similar temperature. OGTT was carried out and the 3-dB bandwidth changes of resonance peaks were measured and correlated with reference glucose concentration. 100% data points fell in Zone A and B of CEG.

4. Conclusion and outlook

Researchers never stop to pursuit the ultimate solution for noninvasive blood or ISF glucose monitoring, driven by the tremendous academic and market values. EM wave based methods are the most attractive ones owing to its wide spectral region and rich information contained. We listed several representative techniques herein and the corresponding achievements up to now. Although numbers of groups have demonstrated *in vitro* and *in vivo* applications, there is no well-recognized method to conquer the great difficulty so far. Global challenges include sensitivity, specificity, system stability and calibration. For example, IR and PA spectroscopy often rely on powerful light source with wide wavelength range as well as the advanced calibration methods like PCR and ANN to achieve specificity. Moreover, the penetration depth is also limited due to the strong tissue absorption in this region. Microwave can reach deeper tissue but there is no specific absorption for glucose. In another word, it lacks specificity. Raman spectroscopy possesses favorable specificity. Nevertheless, its sensitivity is poor and the system is relatively complex. Fluorescence based method has prominent sensitivity and specificity except that it often requires exogenous markers and is not truly noninvasive. Despite that requirements have yet to be met for these novel approaches to replace the current finger-prick glucose meters, researchers keep exploring unknown area and overcoming

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existing challenges. With development in multiple fields such as laser technology and Terahertz technology, the long-standing issue of noninvasive glucose monitoring is expected to be solved with interdisciplinary techniques.

Conflicts of Interest: The authors declare no conflict of interest.

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