DIABETES could be a common life-long condition wherever the degree of glucose within the body measure too high as a result of the body is unable to convert it to energy as a result of insufficient internal secretion or the internal secretion not functioning properly. Currently people with diabetes monitor their blood glucose by drawing blood through a finger prick then using a hand-held glucose meter. However, this method is generally discomfort due to the pain and inconvenience for patients. The development of a secure and reliable non-invasive glucose monitor may provide patients with an alternative, painless method. The deviation of continuous glucose monitoring (CGM) information from reference glucose measurements is substantial, and adequate signal processing is needed to scale back the discrepancy between subcutaneous glucose and blood glucose values. The aim of this paper was to study the drawbacks and impact of algorithmic rule for the process and calibration of continuous subcutaneous glucose monitoring data with high accuracy and short delay.

KEYWORDS: Diabetes, Health Monitoring, Noninvasive, Disruptive Technology, Continuous glucose monitoring system.

I. INTRODUCTION

Currently the self-monitoring of blood glucose level in the body to measure draw blood via a finger prick, then use tests strips and a hand-held glucose meter to measure their glucose levels. However, this invasive method is generally disliked due to the pain and inconvenience associated with finger pricking. The development of a non-invasive continuous glucose monitoring (NICGM) technology may provide people with diabetes with an alternative method. Effective diabetes management reduces the risk of long-term complications associated with the disease, which include heart disease, blindness, stroke, kidney disease and amputations leading to disability and premature mortality. The risk of complications is highly reduced with treatment that maintains the circulating glucose levels to as near as normal as possible, thus reducing tissue damage. Monitoring blood glucose levels helps people with diabetes and their carers make informed decisions about their diet, activity and medication requirements, such as insulin dose (1). It can also help patients, carers and their healthcare team alters treatment to help prevent long-term complications. The conventional way for people with diabetes to test their blood glucose levels is through a portable device known as a blood glucose meter. First, the side of a finger is pricked using a lancet to draw a small drop of blood. The blood is then transferred to a test strip which is inserted into the blood glucose meter, which then provides a result. Devices that can monitor glucose continuously and automatically are also available, and are known as “continuous glucose monitors” (CGM) or real-time CGM. A typical system includes:

1. A disposable glucose sensor placed just under the skin and worn for a few days until replacement;
2. A link from the sensor to a non-implanted transmitter which communicates to a radio receiver; and
3. An electronic reader/receiver worn like a pager that records and displays glucose levels.

II. NON-INVASIVE GLUCOSE MONITORS

NICGM technologies monitor glucose levels without compromising the skin barrier. These technologies aim to provide continuous readings similar to the currently used CGMs, or intermittent readings where patient activity is necessary to perform the test. We framed a search strategy to identify new and emerging NICGM technologies using the following sources:

- Technology databases,
- Clinical trial registries,
- Bibliographic databases,
- Relevant conferences reports and abstracts,
- Review articles and commentaries in relevant specialist journals.

These searches were done by searching more general sources of information, such as Google, health media reports and industry news. From the results we classified three general categories of techniques for measuring glucose levels were identified:

- Optical techniques
- Electrochemical techniques

These techniques have some specific techniques and its have sub division and different methods are available to monitor the glucose level in the body.

Table 1: Non-invasive glucose monitoring technique and number of techniques

<table>
<thead>
<tr>
<th>General Technique</th>
<th>Specific techniques</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optical techniques</td>
<td>Absorption spectroscopy</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Raman spectroscopy</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Fluorescence</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Surface plasmon resonance interferometry</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Optical coherence tomography</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Photoacoustic spectroscopy</td>
<td>1</td>
</tr>
<tr>
<td>Transdermal techniques</td>
<td>Impedance spectroscopy</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Reverse iontophoresis</td>
<td>5</td>
</tr>
<tr>
<td>Electrochemical techniques</td>
<td>Enzymatic detection of glucose</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Amperometry</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>Refractive changes in the eye</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Ultrasonic, electromagnetic and heat capacity</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Micro sensor and computer technology</td>
<td>1</td>
</tr>
</tbody>
</table>

OPTICAL TECHNIQUES utilize the different properties of light to interact with glucose in a concentration-dependent manner. Within this type there were a number of techniques identified that were apparent in the emerging NICGM technologies:

Absorption spectroscopy is employed as an analytical chemistry tool to identify the presence of a particular substance in a sample, and in many cases, to quantify the amount of the substance present.

Technology (breath, intermittent).

Relevant types of absorption spectroscopy include:

1. Near-infrared absorption spectroscopy (NIR) which uses a beam of light with a wavelength in the range of 600-2,500nm, which is focused on the body to determine the concentration of glucose within the tissues.

2. Mid-infrared absorption spectroscopy (MIR) which uses a beam of light...
with wavelength in the range of 2,500-10,000nm. It is based on the same principles as NIR but has low scattering and increased absorption (high wavelength).

Technology (Ball of thumb, index finger, palm below the little finger, ear lobe, intermitter).

Technology (palm, intermitter).

Raman spectroscopy assesses the scattering of single wavelength of light. This is dependent on rotational or vibrational energy states within a molecule.

Technology 6 (finger, intermitter).

Technology 7 (arm or finger, intermitter).

Technology 29 (wrist, continuous).

Technology 36 (finger, continuous).

Photacoustic spectroscopy uses the principle that absorption of light causes ultrasonic waves. The tissue is illuminated by a light source at a specific wavelength and the absorbed energy results in localized heating. The small temperature change (high) results in volumetric expansion which causes an ultrasound pulse to be generated and this can be detected(3). It is suggested that high tissue glucose concentrations reduce the heat capacity of a tissue and as a result increases the velocity of the generated pulse. Technology 10 (ear, intermitter).

Optical coherence tomography (OCT) systems use a low-power laser source, an in-depth scanning system, a sampling device and a light detector. OCT determines the amount of glucose present by assessing the intensity of the reflected/scattered and transmitted light upon interaction with the subcutaneous tissue glucose concentration. Technology (eye, intermitter).

Fluorescence demand the absorption of light at a high wavelength and the emission of light at a second, less energetic wavelength.

Technology (finger, intermitter).

Technology (abdomen or upper arm, continuous).

Technology (finger, continuous).

Technology 39 (eye, continuous).

V. HEALTHCARE PROFESSIONALS’ PERSPECTIVE

In this section we present a summary of comments made by the healthcare professionals on the NICGM technologies identified.

**Accuracy of the Technology and the Technique Used:**
Most of the healthcare professionals hesitate to comment on the accuracy of the technology and the technique used for measuring glucose levels. This was due to there being “little evidence available” as well as the development stages of most technologies being “too early” to accurately comment. Specific concerns were that the techniques used seemed “too indirect to satisfy the demanding standards which would be required, for instance, by driving regulatory authorities” and that some of the methods used “would be affected by how quickly the glucose changes compared to the capillary”,

**Technology Innovation:** All the healthcare professionals agreed that all of the technologies identified were innovative. Comments included “Not many non-invasive devices currently in development use radio wave spectroscopy” and “It’s innovative because it lasts for so long and is accurate”.

**Technology Impact:** “The features of the technology may have a big quality of life impact on patients. It may reduce complications and ambulance call outs” “The reduced financial burden on the NHS in the future could be big if these types of technologies (NICGMs) work” “This is well liked because it’s quick, displays arrows, displays line graph, simple to learn (for patient and healthcare), simple to insert, handset has a long battery life, typically does not need re-charging for 2 weeks, and also has a built in blood glucose meter – so any reading that seems wrong can quickly be checked”

IV. PATIENTS AND CARERS PERSPECTIVE

Patients and carers provided comments around possible barriers that may prevent the adoption of a technology.

**Accuracy:** There were doubts about “whether fluorescence will be reliable based on individual skin tissue characteristics”, “the lag between blood and ocular fluid so am not keen on any tear-based technology” and also “a time lag with this fluid (interstitial) so not as accurate a reading as capillary blood which is not great if hypo”.

**Safety:** Issues raised included “the risk of using lasers on my skin over the long term”, “risks with using infrared over a prolonged period of time”, “the idea of a portable sensor doesn’t sound very safe” and “the transdermal nature makes me weary of skin injury” and the lack of information on “alarms for hypoglycaemia and hyperglycaemia”.

**Ease of use:** Concerns were raised about “whether you would have to put the gel on your skin every time you need to get a reading. I can’t see my teenager doing that every time”, “keeping a small child still for long enough to do this”, “the idea of having to recharge the watch every 24 hours”, “a 10 minute application process sounding inconvenient”, whether “one child/teen who would allow anyone to insert anything into their eyes” and being “bothered to take it [contact lens] out very night and clean it and reinsert in the morning”.

**Discreteness:** Concerns about the visibility of the product were raised including “this sounds big – I don’t want any more big equipment”, “an earlobe sensor would be continuously on display”, “This sounds very discreet – I would feel uncomfortable doing this in public [licking a plastic lollipop stick]” and “I wouldn’t wear something on my finger continuously unless it was very discreet”. Time to results: Products that reported slower result times were not popular: “If this was more than 5 seconds, I would say there is little value compared to finger sticks” and “A minute seems a long time to wait for a result”.

**V. CGM SENSORS**
Continuous glucose monitoring (CGM) sensors are easily allowed measuring the glucose concentration continuously for several days. CGM sensors are composed of three main elements: (i) a needle-based sensor, which is usually inserted in the abdominal containing mostly fat and connective tissue and measures an electrical signal proportional to the glucose concentration present in the interstitial fluid; (ii) a transmitter, which is applied over the sensor and is aimed at transmitting the signal; and (iii) a portable device, which receives the signal and visualizes it on a monitor. The final signal is a glucose concentration, and it is getting by converting the raw electrical signal measured by the sensor through the calibration procedure that exploits one or more reference blood glucose (BG) values collected using a portable self-monitoring (SMBG) device. The calibration can take place neither in the transmitter nor in the receiver. Furthermore, because of the skin-sensor interactions and possible variability of sensor sensitivity over time, CGM sensors require re-calibration every 12 hour.

**VI. CONTINUOUS GLUCOSE MONITORING ALGORITHM**
The algorithm includes the main elements in Figure 1. It operates on the ISIG which is the raw current measured by the CGM sensor with a sampling frequency of 1 per minute.

The newly developed algorithm is described in detail in our previous work. Therefore, to keep this section concise, only a brief description of the algorithm is given.

The rate-limiting filter applies a limit on the signal rate of change, set on a physiological threshold of 4 mg/dl/min. If the rate of change between 2 successive ISIG values exceeds the defined limit, the most recent ISIG (interstitial signal) value is replaced by a weighted local polynomial regression estimate. In the second block, first, the number of zero crossings (ZCs) of the signal first-order differences is calculated in 5-minute segments of the signal. The signal segment is considered noisy if the number of ZCs is > 1. Second, the noisy segments of the signal are filtered by a weighted moving average order of 50. Finally, in the third block, the current measured by the sensor, which is processed in the preceding blocks, is converted into a glucose level (mg/dl) (2). The signal is calibrated by a 2-point calibration approach, coefficients being estimated using robust regression with a bi-square weight function. A maximum of 4 BG-ISIG pairs and a minimum of 2 pairs per day are utilized for calibration, forming the calibration set. The calibration set is corrected for any existing low correlation coefficients between reference BG measurements and ISIG values and also for a low relative standard deviation (RSD) of the BG value(s). A corrective intercept (CI) as described by Mahmoudi et al is subtracted from the calibrated sensor glucose (SG) to correct the overestimation of BG by CGM in the hypoglycemic range of BG (BG ≤ 70 mg/dl).

\[
\text{ISIG} = \text{lg} + \text{R0}
\]

Where ISIG (interstitial signal) is the current measured by the sensor, \(\text{lg}\) is the true glucose current, and \(\text{R0}\) is the sensor background current.

**Figure: 1 algorithm for processing of continuous glucose monitoring data**

The rate-limiting filter applies a limit on the signal rate of change, set on a physiological threshold of 4 mg/dl/min. If the rate of change between 2 successive ISIG values exceeds the defined limit, the most recent ISIG (interstitial signal) value is replaced by a weighted local polynomial regression estimate. In the second block, the number of zero crossings (ZCs) of the signal first-order differences is calculated in 5-minute segments of the signal. The signal segment is considered noisy if the number of ZCs is > 1. Second, the noisy segments of the signal are filtered by a weighted moving average order of 50. Finally, in the third block, the current measured by the sensor, which is processed in the preceding blocks, is converted into a glucose level (mg/dl) (2). The signal is calibrated by a 2-point calibration approach, coefficients being estimated using robust regression with a bi-square weight function. A maximum of 4 BG-ISIG pairs and a minimum of 2 pairs per day are utilized for calibration, forming the calibration set. The calibration set is corrected for any existing low correlation coefficients between reference BG measurements and ISIG values and also for a low relative standard deviation (RSD) of the BG value(s). A corrective intercept (CI) as described by Mahmoudi et al is subtracted from the calibrated sensor glucose (SG) to correct the overestimation of BG by CGM in the hypoglycemic range of BG (BG ≤ 70 mg/dl).
data, i.e., reducing the random noise component overlapped to the true glycemic signal; (ii) improving the accuracy, reduction or even elimination of the systematic differences (i.e., biases and time-drifts) observable between CGM data and gold-standard BG measurements due, e.g., to imperfect sensor calibration or variability in time of sensor sensitivity; and (iii) improving the timeliness of CGM hypo/hyperglycemic alerts by predicting the future BG concentration and generating the prevention of hypo/hyperglycemic alerts(11).

Figure 3: Input source of sensor

Sensor output signal may interrupt or change due to variety of following factors:

- Interfering or modifying variables (i.e., temperature)
- Drift (i.e., changes in chemical structure or mechanical stresses)
- The measurement process changes the measurand (i.e., loading errors)
- The transmission process changes the signal (i.e., attenuation)
- Human observers (i.e., parallax errors)

Systematic errors can be corrected with compensation methods (i.e., feedback, filtering).

Numerous methods have been proposed for measurement of accuracy and precision of CGM and SMBG. The precision and accuracy, usually measured by %MARD, can vary dramatically in a smooth relationship with glucose levels. These three key challenges have been overcome by the creation of the algorithmically “smart” CGM sensor, which consists of placing, in a cascade of the output of a commercial CGM sensor, three software modules for (i) denoising; (ii) enhancement; and (iii) prediction. The denoising module is aimed at reducing the uncertainty due to measurement noise on CGM data by exploiting real-time digital filters. The goal of the enhancement module is improving the accuracy of CGM data by reducing systematic differences between reference BG measurements and CGM data due to, for example, BG-to-interstitial glucose (IG) kinetics and/or variability in time of CGM sensor sensitivity(6).

Finally, the prediction module is aimed at mitigating the occurrence of hypo/hyperglycemic events by

VII. PITFALL OF EXISTING ALGORITHMS IN CGMS

In the previous algorithms such as CGMS gold, G4 platinum continuous glucose monitor presents a problem of lack of accuracy, especially in the lower range, sometimes leading to missed or false alarms(10). Due to the sensor sensitivity and external inputs to the original signal it may happen.

Figure 2: Signal conversion of sensor

As reviewed in Sparacino et al. the main past challenges were related to the improvement of the quality of the data coming from CGM devices via suitable signal processing methods. In fact, even if CGM sensors were considered to be innovative devices for glucose monitoring, the limited exactness and reliability of CGM data represented a holdup for both the daily use of CGM in the clinical practice and the development of CGM-based applications(4). The evolution over the last 15 years of CGM accuracy, calculated as mean absolute relative deviation (MARD) with respect to very precise and accurate BG reference measurements, of some of the most important commercial CGM sensors, is shown in Figure 3. As is visible, at the time of writing the work, the accuracy of commercial CGM sensors was significantly higher than the nominal SMBG systems. In particular, the following three main areas were identified as the keys to enhancing CGM sensor performance: (i) improving the precision of CGM data, i.e., reducing the random noise component overlapped to the true glycemic signal; (ii) improving the accuracy, reduction or even elimination of the systematic differences (i.e., biases and time-drifts) observable between CGM data and gold-standard BG measurements due, e.g., to imperfect sensor calibration or variability in time of sensor sensitivity; and (iii) improving the timeliness of CGM hypo/hyperglycemic alerts by predicting the future BG concentration and generating the prevention of hypo/hyperglycemic alerts(11).
VIII. CONCLUSION

In this paper we discussed noninvasive monitoring techniques, users and carer perspective of BG measuring device, general step of algorithm, calibration methods and pitfall analysis of existing methods towards a futuristic research. Blood glucose measuring value by CGMS devices has error in the method of gold standard BG assay, and CGMS gold. The original CGMS gold algorithm used capillary glucose and valid sensor intensity data, which also affects the calibration accuracy. In the current study, the accuracy of the BG measurements was not assessed by comparing with a gold standard measurement; however, it performed an analysis to indicate the precision of the BG values, by measuring the absolute difference between the 2 capillary BG values taken at each instance. The mean of the absolute differences across the data was 7.7 mg/dl (SD ± 14.3mg/dl)(12). By eliminating external interfering signals in the original glucose value we can get more accuracy and time line data effectively. In future planning to write an Blood Gulcose algorithm name as (PRPM Paul Rodrigues, Pandimurugan) CGMS for better accuracy and short delay.

REFERENCES


