First human experiments with a novel non-invasive, non-optical continuous glucose monitoring system

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Abstract

This paper describes a non-invasive continuous glucose monitoring system based on impedance spectroscopy. Changes in the glucose concentrations can be monitored by varying the frequency in the radio band over a range, optimised to measure the impact of glucose on the impedance pattern. A number of clinical-experimental studies (hyperglycaemic excursions) were performed with healthy subjects in order to prove the applicability of this approach. The sensor used in these experiments is the size of a wristwatch and holds an open resonant circuit coupled to the skin and a circuit, performing an impedance measurement. In most cases, the experiments showed a good correlation between changes in blood glucose and the sensor recordings. A detailed description of the trials is presented. The results of this first series of experiments can be considered as a proof of concept for this novel non-invasive monitoring approach. Nevertheless, partly due to the indirect measurement, a considerable number of questions remain to be clarified.

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1. Introduction

It is well known, that all types of diabetes are characterized by disturbances in carbohydrate metabolism, high levels of blood glucose and, in the long-term, risk of a wide spectrum of severe complications affecting many body tissues and organs. Tight metabolic control, using frequent blood glucose measurements by means of blood glucose meters, can guide the administration of insulin and decrease the possibility of the long-term complications of diabetes. However, it is difficult to maintain near normoglycaemia in people with type 1 diabetes, without blood glucose concentrations declining frequently to low levels, inducing hypoglycaemic events. There is a need for a glucose monitoring system that can provide detailed information on glucose patterns throughout the day (Tamada et al., 1999). In addition, such a system provides an opportunity to sound alarms for rapid declines in blood glucose values, in order to reduce the risk of hypoglycaemic events (Marks, 1996; Grafenstein and Duchna, 1985). A number of alternative strategies, including implanted glucose sensors, tissue fluid sampling and non-invasive technologies, are being under development to allow pain free glucose monitoring.

Non-invasive glucose monitoring is clearly the most attractive approach for patients with diabetes, allowing more frequent, at best even continuous, measurements without any pain or sensation. Such a system should also lead to a reduction in the number of undiscovered hypoglycaemic events (Marks, 1996), as well as in the number of episodes and length of hyperglycaemic periods. There are four categories of non-invasive
glucose monitoring technologies, involving electromagnetic waves in development (Klonoff, 1997; Uemura et al., 1999; Koschinsky and Heinemann, 2001): near infrared (NIR) spectroscopy, far infrared (FIR) spectroscopy, optical rotation of polarized light and impedance or dielectric spectroscopy (DS). The main difficulties with the first three techniques are the relatively weak changes due to glucose imprinted to the signals registered, the limited resolution and the insufficient precision (Klonoff, 1997; Koschinsky and Heinemann, 2001). The latter one, DS, has been tested over a period of time for non-invasive glucose monitoring.

In complex biological systems, fast as well as ultra-slow molecular rearrangements take place in the presence of microscopic, mesoscopic and macroscopic organisations (Beving and Eriksson, 1994; Kuang and Nelson, 1998). To gain this information, a non-invasive approach such as DS can be used. DS has a unique standing among numerous modern methods used for physical and chemical analyses of material, because it can investigate the relaxation processes of complex systems in an extremely wide range of characteristic times from 10^{-12} to 10^{14}\,\text{s}. DS is especially sensitive to intermolecular interactions and, is able to monitor cooperative processes. It provides a link between the investigation—via molecular spectroscopy—of the properties of the individual constituents of complex biological material and the characterization of its bulk properties (Grant et al., 1978; Schwan and Morowitz, 1962; Pethig, 1979; Grimes and Martinsen, 2000; Takashima et al., 1989).

It is well known, that glucose does not affect the dielectric spectrum in the MHz frequency band (Fuchs and Kaatze, 2001), and this is the reason its concentration cannot be measured directly. However, because of the specific reactions of blood and tissue cells to varying glucose concentrations, the electrolyte balance across the membranes of blood and underlying tissue is changed. This is the reason why both AC and DC conductivity are sensitive to these subtle changes in electrolyte balance, which is related to the blood's glucose levels (Hayashi et al., 2002).

The correct frequency has to be chosen in order to develop a glucose sensor based on DS that will be sensitive to the electrical changes in the body, particularly in blood. As mentioned, glucose changes in blood are accompanied by significant conductivity variations, which considerably influence the effect of electric polarization of cell membranes (β-process). This is the reason why the working frequency interval should not be too high so as not to lose the sensitivity to the β-dispersion and ionic DC conductivity (<200 MHz). At the same time, the frequency range should not be too low so as not to have problems with electrode polarization and huge signals from the α-dispersion in tissues (>100 KHz). For this reason, we chose a frequency range between 1 and 200 MHz.

2. Experiments

2.1. Sensor

The sensor uses electromagnetic waves in the selected frequency band that interact with the skin and underlying tissue, to be able to monitor its electrical properties. This is the reason why the sensor can be represented as a serial resonate contour terminated to the working capacitance. The impedance of the sensor at a given resonance frequency depends on impedance changes within the human skin and underlying tissue. The equivalent circuit of the sensor mounted on the skin is presented in Fig. 1. The impedance of this RLC resonant circuit is measured over the specified frequency range by means of a VNA (Vector Network Analyser) or a resistive divider.

The typical impedance behaviour of the sensor attached to the skin of a patient at different times when significant changes of blood glucose have been induced is shown in Fig. 2.

The data shown in Fig. 2 were obtained by means of a VNA HP 8753E (Hewlett Packard, 1997) in the frequency range of 1–200 MHz. Fig. 2 presents frequency changes of the modulus |Z| and the phase of the impedance. It shows that the resonance frequency, the minimum of |Z|, as well as the Q factor of the resonant circuit changes with different blood glucose concentrations. In the defined frequency range, the described sensor can therefore provide sensitive measurements of the electrical properties of the skin and the underlying tissue. The sensitivity of the signal was between 20 and 60 mg dl^{-1} Glucose/Ω.

The impedance, in the case of the non-invasive portable glucose sensor, is measured in the same frequency interval by means of a resistive divider (see Fig. 3). A specifically designed stable, low harmonics Voltage Controlled Oscillator (VCO), with uniform amplitude (<0.3 V) over the whole frequency range,

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Fig. 1. A simple electrical model of the sensor mounted on the skin. L is the inductance of the external coil, C is the fringing capacitance of the sensor attached to the skin and R is the averaged resistance of the skin and underlying tissue.
sweeps through the selected frequency band in steps of \( \Delta f = 0.1 \) MHz. The VCO voltage \( U_{\text{Ref}} \) is fed over the series resistance \( R_s \) to the sensor impedance \( Z \), where the sensor voltage \( U_{\text{Sens}} \) is measured.

The impedance can then be approximated as follows:

\[
Z_{\text{Sens}} \approx R_s \frac{U_{\text{Sens}}}{U_{\text{Ref}} - U_{\text{Sens}}}
\]

This approximation allows the measurement of the phase between the voltages \( U_{\text{Ref}} \) and \( U_{\text{Sens}} \) to be avoided.

### 2.1.1. Portable device and data acquisition circuit

The block-diagram of the registration and data acquisition system of our glucose sensor system is shown in Fig. 3. The analogue part performs a frequency sweep (generated by a VCO) around the resonance frequency of the sensor and detects the amplitude changes. The amplified and filtered output sine wave is fed to the resonant circuit \( Z \) over a discrete resistor \( R_s \) to form a resistive divider. Amplitude detection is performed on the source voltage, as well as the divided voltage and is transferred to an Analogue- to Digital- (AD) converter. Since the impedance of the sensor is temperature dependent, a temperature sensor mounted inside the sensor performs a temperature measurement.

The digital part (lower part in Fig. 4) controls the measurement and operates the user interface. Its main part is the micro controller. It turns the analogue circuit on and off, controls the frequency sweep of the VCO by an external Digital- to Analogue- (DA) converter and converts the amplitude voltages and temperature reading to digital values using the internal AD converter. The measured values are stored into the trace memory.

The device is powered by a rechargeable battery, which lasts for 4 days at 1 min measurement cycle. The data can be presented on a display or read out to a computer by means of a serial interface.

### 2.1.2. Data processing

The data processing is performed as illustrated in Fig. 5.

A frequency sweep and a temperature measurement are performed every minute. The voltage amplitude is measured at 375 points of the scanned frequency. Experiments showed, that measuring every minute is sufficiently frequent, even though the sensor would allow 4 times more sweeps to be taken to track glucose variations continuously. The impedance minima \( |Z|_{\text{min}} \) will be considered as the sensor signal in all further presentations. The raw data is downloaded to a PC in...
order to estimate the time dependencies of $|Z|_{\min}$. In this paper only raw data versus time, superimposed with invasive blood glucose measurements, are presented.

### 2.2. Glucose clamp technique

A number of in-vivo clinical-experimental studies were performed with healthy subjects. Subjects fasted, apart from water, for 8 h before the experiments. The local ethics committee approved the study protocols. The studies were carried out according to the declaration of Helsinki. The subjects were restricted from excessive physical activities and the intake of alcohol for 24 h prior to each study day.

The whole scheme of the three trials could be presented in **Fig. 6**:

The experimental set-up employed in the studies has been described in detail elsewhere, in brief the procedure was as follows: A 17-gauge PTFE catheter was inserted into an antecubital vein for blood sampling. This line was kept patent with 0.15 mol l$^{-1}$ saline. A dorsal hand vein was cannulated in retrograde fashion for insertion of an 18-gauge PTFE double lumen catheter, which was connected to the glucose sensor of a Biostator (glucose controlled insulin infusion system—GCIIS, MTB Medizintechnik, Ulm, Germany).

A third vein was cannulated with an 18-gauge PTFE catheter on the contralateral arm to infuse glucose (20% in water), saline and somatostatin. An insulin solution was infused continuously into the same vein by means of a syringe pump (Perfusor Secura FT; B. Braun Melsungen, Germany). Baseline infusion of somatostatin suppressed the endogenous insulin secretion of the studied healthy subjects. The Biostator keeps blood glucose constant at a given target level. The glucose clamp algorithm is used by the Biostator for calculation of the glucose infusion rate necessary to keep blood glucose constant. It is based on the result of the current blood glucose measurement and the grade of variability of blood glucose in the minutes before. During the experiments the subjects were under continuous observation and all eventual adverse events were documented.

In all experiments the sensor system was fixed at the wrist of the left arm according to **Fig. 6**, by means of an
expandable band, keeping the device on the same spot for the time of the experiment. No adhesive materials were used.

Temperature, blood glucose, insulin infusion rates and somatostatin infusion rates were closely monitored and registered during each experiment.

The room temperature was controlled and kept at 23 °C. Each experiment typically lasted 10 h, under the standard configuration and conditions described above.

Different blood glucose profiles were studied according the study protocols outlined in Fig. 7.

The following sets of glucose clamp experiments were performed.

2.3. First series of experiments

In a first set of experiments blood glucose was varied according to a simple or more complex manner. In order to evaluate how well the sensor signals correlate with changes in blood glucose or glucose in the interstitial fluid (ISF) during a glucose clamp, blood glucose and glucose changes in ISF were measured. This was carried out by a microdialysis catheter (CMA-60 CMA Microdialyses AB, Stockholm, Sweden), abdominally placed in the subcutaneous tissue. Glucose measurements with this system are known to have a time lag when blood glucose is changed (Thennadil et al., 2001; Stout et al., 2001). Blood glucose was increased rapidly in eight healthy subjects from euglycaemic (100 mg dl⁻¹) to hyperglycaemic values (300 mg dl⁻¹) according to the simple or more complex glucose profiles given in Fig. 7.

2.4. Second series of experiments

During a typical glucose clamp experiment, considerable volumes (2–3 l) of fluids are infused intravenously into the human body. Another series of experiments was performed where glucose was administered orally to examine whether there is a difference in the sensor signal recordings compared to the situation when glucose is administered intravenously. Changes in blood glucose can be controlled less with oral administration, resulting in a single peak in the glucose profile.

A slow increase from euglycaemic to hyperglycaemic values from 100 to 300 mg dl⁻¹ was induced in four...
healthy subjects by means of an oral glucose load (Fig. 7), with a baseline infusion of somatostatin to suppress endogenous insulin secretion.

2.5. Third series of experiments

In the last series of experiments the sensor signals over time were registered while blood glucose remained unchanged. Blood glucose was kept constant for 8 h in four healthy subjects in order to study changes in the impedance pattern, which might occur over time due to other reasons.

3. Results and discussion

3.1. First series of experiments

A good correlation between changes in blood glucose and sensor recordings was obtained in five out of eight experiments. Results of a single experiment measured

Fig. 8. Sensor signal compared to blood glucose and interstitial fluid (ISF) glucose levels during glucose clamps with glucose administered intravenously. — sensor signal \( [Z] \), —interstitial fluid glucose levels measured by means of the CMA-60 microdialyses technique (mg dl\(^{-1}\)); □, \( [Z] \) blood glucose continuously measured by the Biostator (mg dl\(^{-1}\)).
with the first prototype are given in Fig. 8. The sensor signals were processed according to the procedure displayed in Fig. 5 and superimposed as raw data onto the blood glucose profile (no curve fitting was carried out). The profile for the glucose changes in interstitial fluid is superimposed as well, showing the typical lag time between changes of glucose in blood and interstitial fluid.

An equilibration process typically characterizes the first 60 min of signal recordings. After that, the sensor signal closely follows changes in blood glucose. The raw signals were not subject to any noise reduction or smoothing process. Since the subjects moved their arms fairly often, the sensor was moving as well. This resulted in a rather noisy signal with level shifts shortly after 9:12 h and before 16:24 h, being recorded. Mathematical treatment of this signal would obviously result in a noise reduction and correction of level shifts. This was not carried out here in order to present the raw data as recorded by the device.

With the high rate of change of blood glucose during the glucose clamps, applied for single glucose changes, the sensor signal suggests to track variations of glucose in blood rather than in interstitial fluid.

3.2. Second series of experiments

In this series three out of four experiments showed a good correlation between changes in blood glucose and the sensor recordings induced by oral glucose administration. A typical result of an individual experiment can be seen in Fig. 9. Again, the raw sensor signals were processed according to Fig. 5 and superimposed as raw data onto the blood glucose profile. After the equilibration process of about 60 min, the sensor signal closely follows variations of blood glucose. The raw signals were not processed to reduce noise. However, the noise reduction due to improved electronic is clearly visible. Spikes in the recorded signals shortly before 12:00 h and around 16:00 h are due to short removals of the sensor from the skin, exposing the open resonant circuit to air. Due to the permittivity of air = 1 (human body ca. 80), the impedance minimum is out of the sensor’s measurement range. Such events induce spikes in the raw sensor signals.

This clearly indicates the importance of a good sensor system fixation onto the human skin.

3.3. Third series of experiments

The last set of experiments examined changes of the sensor signal over time under fasting conditions (blood glucose levels held constant at 100 mg dl\(^{-1}\)) (Fig. 10). In three of the four experiments glucose changes could be monitored closely. Only small changes occurred in the sensor signal over time.

3.4. Signal to noise considerations

In the graphs presented in this section it can be seen that the impedance change \( Z \) compared to glucose is rather small. The impedance changes in our experiments are in the range of 0.5–0.8 Ω per 20 mg/dl (about 1 mmol/l). The device has a resolution of better than 0.1 Ω, which means a resolution of 4 mg/dl or better, which is appropriate for continuous glucose monitoring. Therefore, the current devices allows to prove the measurement principle.

In order to improve the signal to noise ratio, which is crucial for the application, the electronic goes through a
major redesign and the basic algorithm presented in this paper is enhanced in order to remove the movement artifacts. Obviously, every glucose value is not only based on a single measurement, but a result of several sequential measurements. Elaborations on the required stand-alone algorithm are beyond the scope of this paper.

4. Conclusion

These first human experiments showed that the glucose sensor system presented allows the monitoring of glucose changes in the skin and underlying tissue, requiring neither skin to be broken nor application of significant radiation into the human body. The signal changes have a closer correlation to glucose changes in blood than to those in interstitial fluid.

The sensor system appears to perform comparably in glucose clamp experiments with i.v. glucose infusion and in experiments where glucose was administered orally.

It is well known that skin parameters e.g. thicknesses of individual layers or moisture content of stratum corneum can vary considerably between different subjects (Martinsen et al., 1997). Recently, it was shown (Martinsen et al., 1999) that most contributions of moisture for example, affects the impedance measured at lower frequencies (< 1 MHz). Even in spite of the fact, that our frequency band was chosen in order not to be too sensitive to these side effects, some contributions still have to be taken into account. So sweat and the relocation of the sensor system are some of the factors that need to be considered in order to obtain a reliable glucose related sensor signal. Variations in temperature also affect the sensors signal since they have an impact on the permittivity of e.g. water. This could be a reason why the three experiments were not performing satisfactorily.

Spikes in the registered signals resulting from e.g. movements, need to be detected and erased once they are identified as invalid measurements by means of mathematical methods. These spikes can, due to i.e. removal of the sensor from the skin, be very big but are therefore also easy to detect and to clip. Besides the spike clipping process, the frequency of the impedance minimum can also be taken into account in order to increase the sensitivity and precision of the system. There was no evidence of any device-related adverse effects.

In summary, these studies show that our impedance spectroscopy approach potentially allows for a truly non-invasive glucose sensor of glucose monitoring in humans to be established. Nevertheless, partly due to the indirect measurement, a considerable number of open questions remain to be clarified.

In order to examine phenomenon’s on the cellular membrane level, we are studying the specific impact of D-glucose on the electrical properties of human cell membranes in vitro by dielectric spectroscopy. We hope these studies will allow further building on the understanding of the observed effects (Hayashi et al., 2002).

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References