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Impedance spectroscopy of solutions at physiological glucose concentrations

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Abstract

Impedance spectroscopy has been proposed as possible approach for non-invasive glycaemia monitoring. However, few quantitative data are reported about impedance variations related to glucose concentration variations, especially below the MHz band. Furthermore, it is not clear whether glucose directly affects the impedance parameters or only indirectly by inducing biochemical phenomena. We investigated the impedance variations in glucose–water, glucose–sodium chloride, and glucose–blood samples, for increasing glucose values (up to 300 mg/dl). In all the frequency range ($0.1–10^7$ Hz) glucose–water samples showed impedance modulus increases for increasing glucose values (up to 135%). In blood and sodium chloride samples the impedance modulus showed only slight variations (2% and 1.4%), but again in wide frequency ranges. Therefore: i) glucose directly affects the impedance parameters of solutions; ii) effects are more relevant at frequencies below the MHz band; iii) the influence on the impedance is decreased in high conductivity solutions, but still clearly present.

Keywords: Dielectric spectroscopy; Blood; Non-invasive; Glycaemia; Diabetes; Monitoring

1. Introduction

In recent years the measurement of tissue and blood impedance through an alternating current has been suggested as a non-invasive approach to determine glycaemia [1]. In [2], it was shown that variations in blood glucose concentration determine significant changes in the impedance of a subject's skin and underlying tissues in a range between 1 and 200 MHz. However, the authors claimed that the observed impedance changes were not due directly to glucose, because the impedance of glucose solutions in pure water is independent by the glucose concentration. The impedance changes were due to biochemical reactions triggered by variations of glucose concentration, which cause variations in the electrolyte balance across the membrane of erythrocytes. In other studies, however, impedance variations were found in glucose–water solutions with different glucose concentrations, even at concentration values that mimic glycaemic levels in human blood [3]. On the other hand, in [3] the impedance differences were observed only in a relatively narrow frequency range.

These partially contradictory results and considerations show that it is not completely clear whether glucose directly affects the impedance behavior of a solution, especially when physiological concentration levels are considered. The aim of this study was to examine possible impedance variations in solutions at different glucose concentrations within the physiological range. We studied glucose solutions both in pure water and in blood in an *in vitro* context. We also studied the sodium chloride 0.9% solution, which has some similarities with blood (for instance, it presents the same osmotic pressure of plasma), but it lacks any cellular component. Special attention was devoted to the analysis of low frequencies, which were poorly investigated in previous studies, especially in blood.

2. Materials and methods

2.1. Preparation of samples

A sample of deionized water (18.5 MΩ cm resistivity, Millipore MilliQ Element system, Billerica MA, USA) was prepared. The same water was used to prepare three glucose–water samples, at glucose concentrations spanning from normal

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glycaemia to that observed in severe diabetes, i.e. 100, 200, 300 mg/dl. Each sample consisted of 50 ml of water. D-glucose (99.5%, Fluka) was added to the water samples to reach the indicated concentrations. The solutions of sodium chloride 0.9% (Baxter) were prepared similarly.

For the preparation of blood samples we collected 500 ml of bovine blood immediately after the animal slaughter. Since it was necessary to prevent both coagulation and glycolysis [4, 5] in the blood container we had previously poured 1 g of potassium oxalate (99.98%, Sigma-Aldrich) and 1.25 g of sodium fluoride (99.99%, Sigma-Aldrich), acting as anticoagulant and glycolytic inhibitor, respectively [6]. We then measured the glucose concentration of the blood sample by two portable glucose meters (Freestyle, TheraSense, and Glucomen, Menarini Diagnostics). We performed two measures for each meter: the average value was 65 mg/dl. Blood was then stored into a refrigerator at 4 °C. In the following hours we checked again the glucose concentration several times: the differences compared to the first measures were always within the precision of the meters, thus confirming that glycolysis was properly inhibited. Then, we properly added D-glucose to obtain blood samples with concentrations similar to those indicated above.

We also tested the condition of erythrocyte cells after the impedance experiments. We used trypan blue dye ($C_{34}H_{24}N_6O_{14}S_4Na_4$) to discriminate living from dead cells. The reactivity of trypan blue is based on the fact that it does not interact with the cell unless the membrane is damaged. Therefore, the dye penetrates the cell membrane of dead cells only, which consequently appear as blue under microscope observation; 10 ml of each sample were centrifuged at 250 g (1200 rpm) for 7 min, the pellet was then resuspended in 5 ml PBS buffer and after 5 min of incubation with trypan blue solution at room temperature, a 1/180 dilution was filled in a Burker's haemocytometer and observed under a microscope at 10× and 20×. All the samples showed that the majority of cells were still alive (at least 90%).

Therefore, we were confident that at the time of the impedance experiments the erythrocytes were in the condition of triggering mechanisms possibly affecting the measured impedance values.

It must be noted that for some of the samples to be studied we prepared three copies, and we evaluated the accuracy in sample preparation by measuring the glucose concentration of each copy: the differences were always within the precision of each meter (<5%). For the impedance analysis we considered the sample copy with glucose concentration in the middle.

2.2. Impedance measurement

Within 72 h from sample preparation we performed the impedance measures through a Solartron 1260 impedance analyzer. For the measurement cell a probe from Delta OHM was chosen (SP06T model). A block diagram of the probe is reported in Fig. 1 (top). The cell is characterized by plain platinum electrodes: four electrodes are present for separation between stimulation and sensing terminals (Fig. 1 (bottom)), thus allowing minimization of possible secondary effects, such as inductance of cables or parasitic capacitances that can influence the accuracy of the impedance measurement [7]. The electrodes are then surrounded by a covering bell: when the cell is immersed into the glass tube containing the solution sample to be studied, the measurement region is delimited and kept constant. The cell also includes a temperature sensor. The cell *k*-factor is 0.7 cm^{-1}.

Through the Solartron 1260 we applied a 100 mV r.m.s. voltage to the outer couple of electrodes. The electric current was read through the inner electrodes. We analyzed the impedance of the samples in the 10^{-1}–10^7 Hz range. The impedance was measured in five frequency points for each decade.

For each sample studied, we performed two independent measures: after the first measure the cell was cleaned before immersing it again into the sample. The impedance values presented for each sample are the average between the two measures. In the frequency range of major interest (Results) the differences between the two measures in a sample were always lower than the differences between the average values of two different samples. For instance, in the blood samples the worst difference between the two measures in a sample was in the order of 0.1 Ω, which was markedly lower than the average difference between samples at different glucose concentrations.

All the impedance measures were performed with the samples at ambient temperature (23 °C with maximum variations of ±0.3 °C). All the measures were corrected through open-short compensation technique.

3. Results

Modulus and phase of the impedance of water, and of glucose–water mixtures, are reported in Fig. 2. The modulus increased for increasing glucose concentration values in a wide

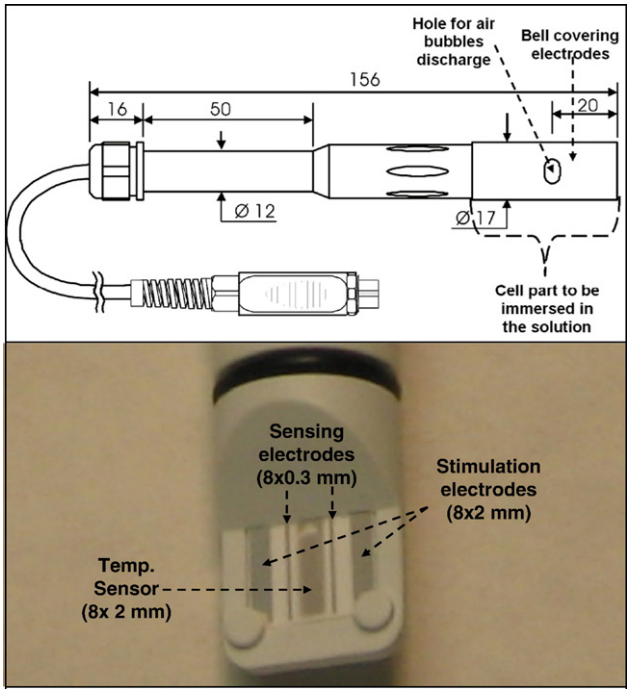

Fig. 1. Block diagram of the measurement cell (top), and photograph of its inner part showing the electrodes (bottom).

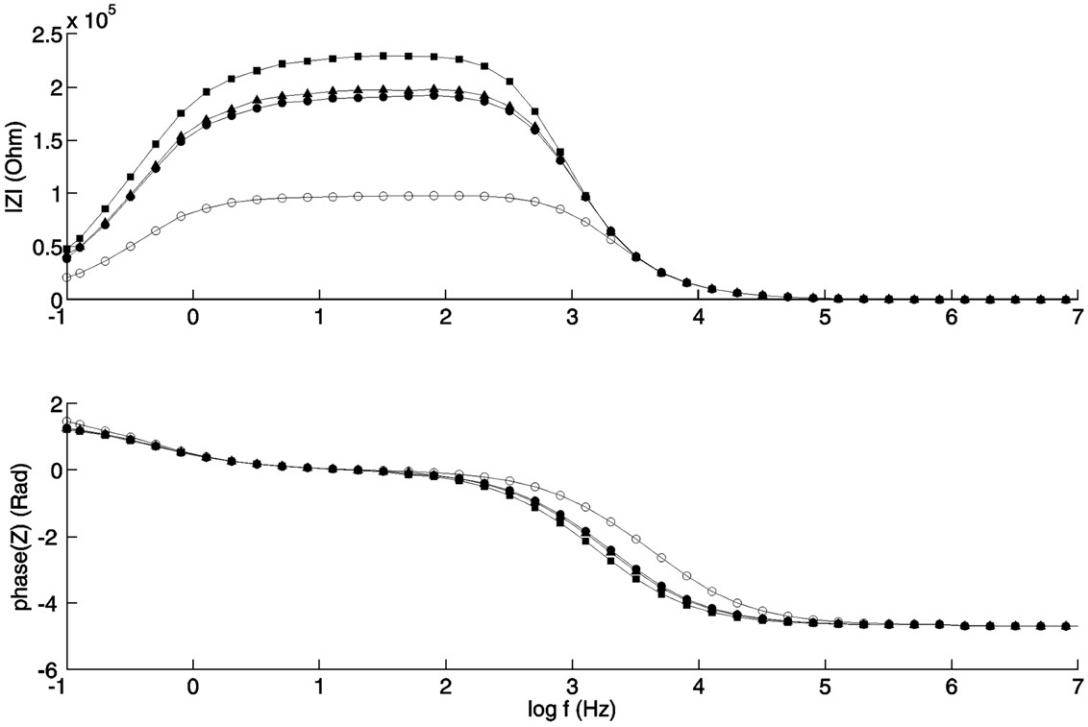

Fig. 2. Impedance modulus (top) and phase (down) for glucose–water samples (empty circle: pure water; full circle: 100 mg/dl glucose; triangle: 200 mg/dl glucose; square: 300 mg/dl glucose).

frequency range, though the variations were nonlinear: an increase step of 100 mg/dl in glucose concentration did not produce impedance variations of the same magnitude (this nonlinearity was observed also in blood and sodium chloride samples, as shown below). The phase decreased for increasing glucose values, though variation was less marked than that observed in the modulus. More precisely, the frequency range where the differences were more evident for the modulus was 0.1–800 Hz (we define it as *reference range*). Outside this range, the differences were less clear, as the modulus curves showed relatively frequent intersections at some frequency values. As regards the phase, the reference range was 80 Hz–10^7 Hz, though from 10^5 Hz onwards the differences were small. Thus, in all the studied frequency range a clear variation in at least one of the two impedance parameters was observed for increasing glucose concentration values. Percentage difference values between the blank sample (i.e. that with no glucose) and that at the highest glucose concentration were reported in Table 1 for both modulus and phase in their own reference ranges.

As regards blood, the impedance of the sample with endogenous glucose only and that of samples with added exogenous glucose is reported in Fig. 3. When looking to the whole modulus and phase curves, almost no variation can be appreciated for the different samples. However, when the analysis was focused on a specific frequency range, some differences emerged. In fact, in a wide frequency range, i.e. 8–$2 \cdot 10^6$ Hz, there was a slight but evident difference in the impedance modulus: similarly to glucose–water samples, the modulus increased for increasing glucose concentrations in the whole range (Fig. 3, top right). Outside the reported reference range, the modulus curves showed frequent intersections. Similar analysis for the phase showed that there was again a relatively wide frequency range, i.e. $2 \cdot 10^5$–$8 \cdot 10^6$ Hz, where a slight phase decrease for increasing glucose concentration was observed in the whole range (not shown). Thus, in a frequency range which almost covers all the studied range at least one between impedance modulus and phase showed clear variations for increasing glucose concentrations. Percentage difference values between the sample with endogenous glucose only and that at the highest glucose concentration were reported again in Table 1.

Glucose–sodium chloride samples showed impedance patterns similar to those observed in blood samples (Fig. 4). Again, some differences in the impedance parameters emerged when a specific frequency range was considered. In the frequency range

Table 1
Mean±standard deviation of percentage difference between the samples at lowest and highest glucose concentration for both modulus and phase in their own frequency reference ranges

	Glucose–water	Glucose–blood	Glucose–sodium chloride
Modulus			
Difference (%)	125±17 [135; 63]	2.00±0.09 [2.24; 1.68]	1.41±0.24 [1.69; 0.56]
Phase			
Difference (%)	43±56 [157; 0.1]	1.51±0.11 [1.60; 1.27]	51±33 [73; 13]
Max. total difference (%)	291	3.69	75
Frequency for max. total difference (Hz)	80	$5.1 \cdot 10^5$	$1.3 \cdot 10^4$

Maximum and minimum percentage differences are reported in square brackets. The maximum total difference (sum of the differences in modulus and phase) is also reported together with the corresponding frequency value.

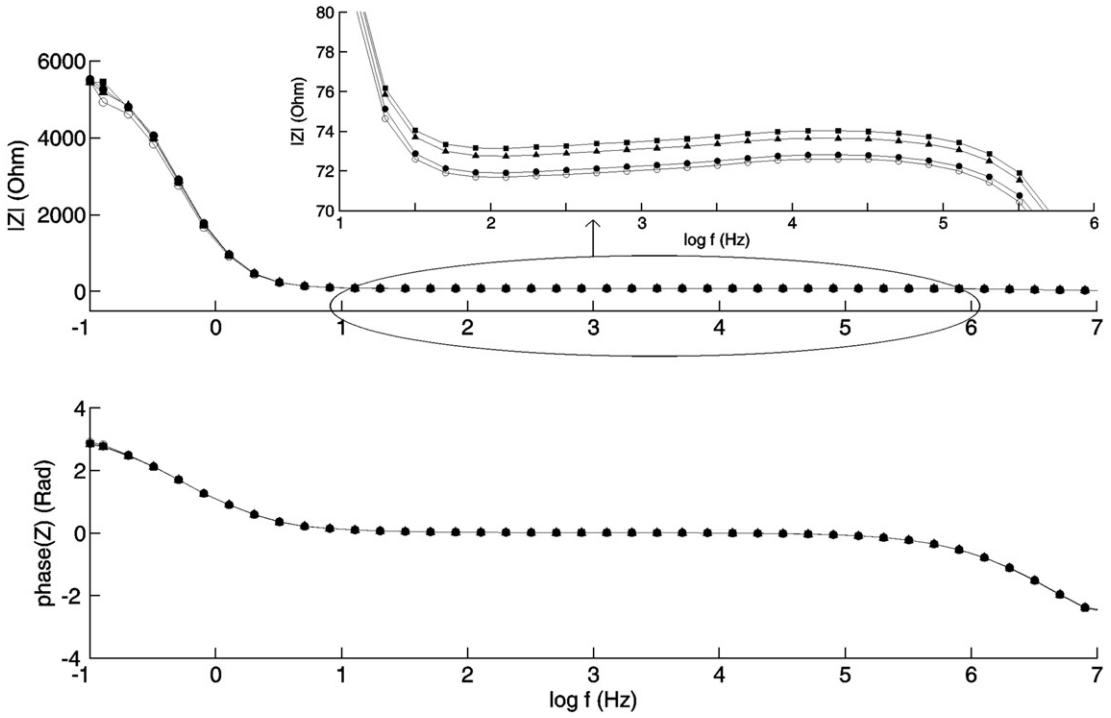

Fig. 3. Impedance modulus (top) and phase (down) for glucose–blood samples (empty circle: blood at basal glucose (65 mg/dl); full circle: 100 mg/dl glucose; triangle: 200 mg/dl glucose; square: 300 mg/dl glucose). Impedance modulus in a portion of the studied frequency range is also reported (top right).

$80–8 \cdot 10^6$ Hz the modulus slightly increased for increasing glucose concentrations in the whole range (Fig. 4, top right), whereas the phase decreased in the $8 \cdot 10^3–2 \cdot 10^4$ Hz range (not shown). Differently to glucose–blood samples, almost all the modulus increase was observed between the first two samples, i.e. the blank sample and that at 100 mg/dl glucose. In fact, the further increase in the modulus value for increasing glucose concentrations was extremely small. Percentage difference

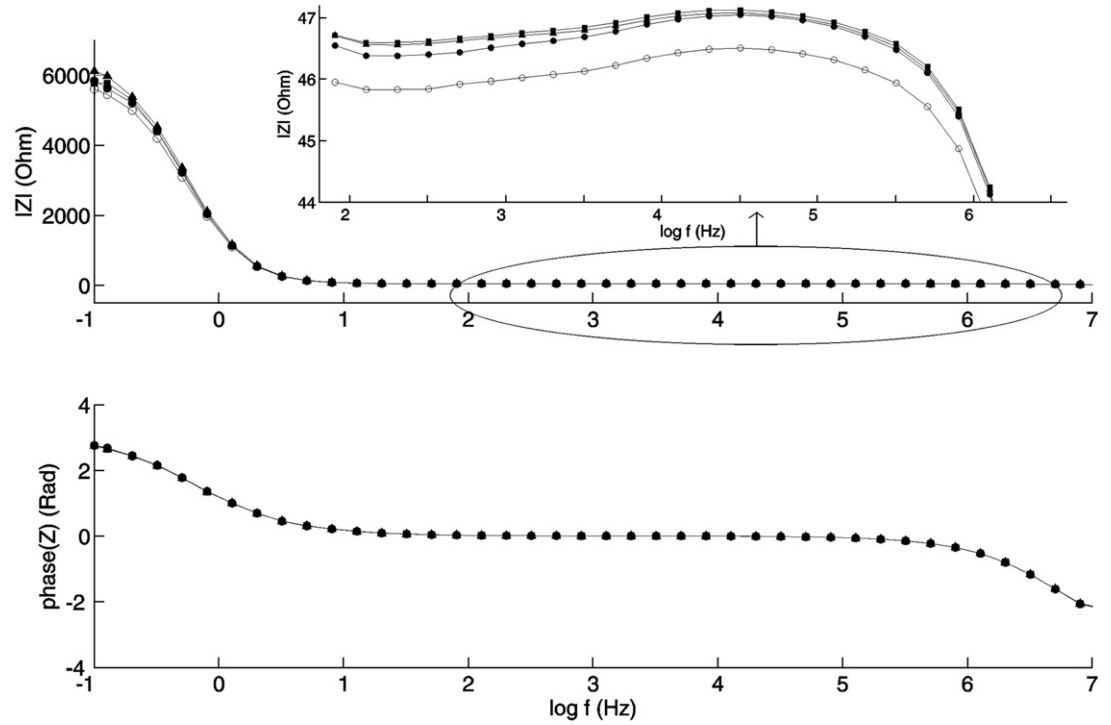

Fig. 4. Impedance modulus (top) and phase (down) for glucose–sodium chloride samples (empty circle: pure sodium chloride 0.9%; full circle: 100 mg/dl glucose; triangle: 200 mg/dl glucose; square: 300 mg/dl glucose). Impedance modulus in a portion of the studied frequency range is also reported (top right).

values between the blank sample and that at the highest glucose concentration were reported again in Table 1. It must be noted that the percentage differences for the phase were very high compared to the results found on glucose–blood samples. However, this finding may be biased by the fact that in the phase reference range the phase value was very low (mean value equal to −0.0021 rad), and small measurement error may have great influence on the computation of the percentage difference, which may result erroneously high.

4. Discussion

In the recent years there has been a continuous effort in the development of new glucose sensors for improved performance in terms of stability or efficiency [8, 9]. In parallel, a different effort has been carried on aimed at the development of techniques for non-invasive glucose measurement [1]. Some of these approaches have lead to the production of non-invasive glucose meters [10], but for several reasons many of them remained at prototype level. The only one available today is the GlucoWatch [11], and it has several drawbacks [10, 12].

A promising approach for non-invasive measurement of glycaemia is impedance spectroscopy. Some device prototypes have been developed based on this approach, and one of them also reached the market [2, 13, 14], but it was withdrawn and the company filed for bankruptcy [15]. A new company seems to be currently working on a similar device [16, 17], but at the moment no device is on the market.

In [2] the authors claimed that the measurement of glycaemia through impedance spectroscopy is possible as variations in blood glucose concentration induce some transportation phenomena of electrolytes through the cell membrane, and that results in variations in the dielectric properties of the medium. The most relevant phenomenon is the plasma sodium concentration lowering in the presence of hyperglycaemia [18, 19]. In [2] it was claimed that these effects are entirely responsible for the impedance variation of blood and underlying tissues, since glucose variations do not directly affect the dielectric properties of the investigated medium in the MHz band, as also stressed in other studies from the same research group [20, 21]. In fact, some references were provided to other studies where the effect of variations in glucose concentration was studied in water [22, 23]. In [23] it was shown that at glucose concentrations lower than 1 g/cc the dielectric properties of the glucose–water solution are not different from those of pure water. However, a more recent study contradicts these findings. In [3] the dielectric properties of glucose–water solutions were found different for glucose concentration values varying within the physiological range. In particular, the impedance modulus increased for increasing glucose concentrations within the 1 kHz–1 MHz band.

The first aim of our study was to reproduce the reported experiments on glucose–water solutions. Our results essentially confirm those of the study [3], but in even wider frequency band: in fact, in all the investigated range, i.e. 0.1 Hz–10 MHz, we observed a significant variation in the impedance modulus, phase, or both, though the greater differences were found for frequencies lower than 100 kHz. Thus, we can claim that variations in glucose concentration even at low values such as physiological ones should directly affect the dielectric properties of a solution, independently from other mechanisms that may be induced by glucose variations. On the other hand, it is confirmed that the impedance variations due to variations in glucose are certainly more evident at low frequencies, and this may partially explain why they were not observed in the studies [22, 23] where frequencies over 1 MHz were considered.

It must also be noted that the partial differences between our results and those of study [3] may be due to the use of a different measurement cell. In fact, we used a four electrodes cell instead of simple two electrodes cell, thus allowing four terminal measurements less prone to noise effects at medium-high frequencies [7]. Furthermore, we used platinum instead of stainless steel electrodes, the latter being more sensitive to the effects of possible reactions with the solution at low frequencies. A limitation of our measurement cell may be the cell *k*-factor value, which was 0.7 cm^{-1}. For impedance measurements in solutions at relatively high conductivity, like blood or sodium chloride 0.9%, higher *k*-factor values may be more adequate, and that may be investigated in future studies.

Few data can be found in the literature on impedance in blood at different frequencies related to glucose concentration values. In [2] some impedance data were reported from an *in vivo* experiment on humans where glycaemia was 100 and 200 mg/dl, though only frequencies above 1 MHz were investigated. It was shown that both impedance modulus and phase were different between the two glucose concentration values in some frequency ranges, and similarly to our results higher values were found for the 200 mg/dl concentration. As regards the modulus, which was the impedance parameter of major interest, it was claimed that the sensitivity to glucose changes was between 20 and 60 mg/dl glucose/Ω, and this was in acceptable agreement to our results, though the sensitivity that we found was slightly lower. In fact, the best sensitivity that we observed for the modulus between the 100 and 200 mg/dl samples was about 110 mg/dl glucose/Ω (100 mg/dl: 72.2 Ω; 200 mg/dl: 73.1 Ω), at frequencies around 1 kHz. In [3] the dielectric properties of blood for different glucose concentrations were studied *in vivo* on hamsters, and variations in the dielectric parameters were observed for glucose concentrations varying between 150 and 300 mg/dl. However, only one frequency value was investigated (10 kHz), and only semi-quantitative results were reported.

In [24] the dielectric properties of blood with glucose varying in a wide range were studied by a sensor made of two induction coils coupled through two glass tubes containing porcine blood. The ratio between the voltages at the two inductors varied for different glucose values. However, despite the wide glucose concentration interval that was studied including also non-physiological values (from 130 mg/dl up to 10 g/dl), the observed differences were weak, being only 17.72% between the extreme values of the glucose interval. In the hypothesis that the voltage ratio variations were linear to glucose variations, for a possible variation in glucose of 100 mg/dl only a 0.18% variation in the output signal would be

observed. Furthermore, results were presented only in a narrow frequency interval (2.4–2.9 MHz). Similar results were found in another study from the same authors [25].

Some studies investigated the dielectric properties for different glucose concentrations of PBS buffers with suspended erythrocytes [20, 21]. In [20] different glucose concentrations were considered ranging from zero to about 400 mg/dl, and the analysis was performed between 10 kHz to 100 MHz. Variations in the dielectric properties of the buffers were found for the different glucose concentrations. However, the dielectric parameters showed a non-monotonic pattern for increasing glucose values, differently to our results. In [21] the analysis was extended to 2 GHz, with similar findings. The authors claimed that this non-monotonic behavior may be due to erythrocytes activities at the membrane level, but no further details were provided.

In our study huge variations in the impedance parameters for different glucose values were observed only in water. This suggests that the ability of glucose to induce variations in the dielectric properties of the solution may depend on the conductivity levels involved. In fact, both in blood and sodium chloride solutions, which have conductivity much higher than water, the impedance variations were modest compared to those in water. That may also explain the slightly higher variations of the impedance modulus (which is probably more relevant than the phase) observed in blood compared to sodium chloride, as the former is slightly less conductive than the latter. However, we cannot exclude that the slightly higher variations in blood may be due to the indirect phenomena involving cells discussed above.

It must be acknowledged that in blood the impedance measures may be affected by the selected approach for sample preparation, and they may be partially biased by the addition of exogenous compounds, i.e. potassium oxalate and sodium fluoride. However, as all the blood samples derived from the same 500 ml blood container (where the blood was treated with potassium oxalate and sodium fluoride), we are confident that possible exogenous compounds effects on the impedance vales were similar in all the blood samples. Thus, these compounds may have affected the absolute impedance values of the samples, but not the relative impedance difference between the samples, and that was of interest in this study.

Despite the findings that variations in glucose concentration induce some impedance changes in blood, the practical utility of such results for non-invasive glycaemia monitoring still remains to be demonstrated. In fact, in this study we did not assess whether the impedance spectroscopy approach may be able to distinguish between glucose concentration values relatively similar, but with very different clinical meaning: for instance, fasting glycaemia of 100 mg/dl is still considered a normal value, whereas 126 mg/dl already indicates overt diabetes. Possible ability of the approach to reveal hypoglycaemic values should also be investigated.

Furthermore, in an *in vivo* context, non-invasiveness implies that blood cannot be directly accessed, and hence the electrodes should be placed in contact with the skin. As a consequence, many confounding factors related to physiological changes in tissues surrounding the blood vessels may be present. For instance, it is known that hyperglycaemia may cause accelerated collagen aging and elastic fiber fraying [1]. Even when focusing on blood vessels alone, other confounding factors for impedance measurements may be possible variations in microcirculation and in blood cell morphology related to hyperglycaemia [1], as well as variations in blood composition and especially hematocrit [26]. Furthermore, the nonlinear variations in the impedance values related to the differences in glucose concentration may be another confounding factor to be addressed with proper calibration curves. Variations in body temperature may also have a relevant effect on the impedance measurements.

A first clue of possible variations in the impedance values due to differences in blood composition came from the study of a second animal, with basal blood glucose concentration of 115 mg/dl (not shown). When the blood sample of this second animal at 300 mg/dl of glucose (obtained again by proper addition of exogenous glucose) was compared to the corresponding sample of the first animal, we found impedance differences comparable to those observed between the samples at different glucose concentrations in each animal. For instance, at 10 kHz the impedance modulus of the 300 mg/dl sample in the first animal was 74.0 Ω, while in the second animal it was 71.3 Ω. This suggests that possible clinical applications of the impedance spectroscopy approach would require calibration over each subject.

It must also be noted that the use of platinum skin electrodes may be extremely expensive for a device aimed at personal domestic monitoring, but the use of other electrode materials, such as stainless steel, may cause electrode polarization phenomena possibly affecting the measurement accuracy. In fact, previous experiences based on impedance spectroscopy for non-invasive glycaemia monitoring showed how much difficult is reaching the ultimate goal [15].

In conclusion, this study investigated the effect of glucose concentration on the impedance of different solutions, i.e. glucose in water, blood, and sodium chloride. Few studies showed the impedance variations of blood for different glucose concentrations within the physiological range, and to our knowledge no study examined in detail the frequency values below the MHz band: this is one of the main novelties of this study. The advantage of focusing on frequency values below the MHz for possible clinical applications may consist in a lower sensitivity to the electromagnetic noise in the environment. Furthermore, there was no study at all on the impedance in glucose and sodium chloride. Although practical applicability of the approach for non-invasive glycaemia monitoring still needs to be proved, this study showed that glucose is able to directly affect the impedance of the investigated samples. In blood, slight but clear impedance variations for different glucose values were observed in a wide frequency range, and especially below 1 MHz. Possible indirect mechanisms involving cells may only contribute to the observed total variations.

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