Characterization of Physiological Glucose Concentration Using Electrical Impedance Spectroscopy

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Abstract

Non-invasive glucose monitoring is crucial for effective diabetes mellitus treatment while a sound correlation of a non-invasive parameter to glucose level variation is quite challenging. This paper presents characterization of glucose concentrations using Electrical Impedance Spectroscopy (EIS) in three different solutions: 1) 0.9% NaCl, 2) Saline (NaCl 1.3gm, KCl 0.75gm, $Na_3C_6H_5O_7$ 1.45gm, D-glucose 6.75gm in 500mL) and 3) Human Blood for every 25mg/dl change of glucose in total 150ml solution. A rectangular current pulse of 1.5s duration with 1mA peak is applied to the solutions and corresponding voltage is acquired across the solutions with Agilent InfiniiVision 7000B Series oscilloscope and Matlab R2011a Instrument Control Toolbox. The circuit proposed for current injection and voltage acquisition requires only two electrodes would reduce electrode polarization and skin irritation greatly which is a major concern in many previous works use generally four electrodes. Experimental results show sound correlation between EIS and blood glucose concentration. It is clearly found from the EIS that the DC impedance of solutions increases linearly with the increment in glucose concentrations.

Keywords: *Electrical Impedance, Impedance Spectroscopy, Non-invasive Glucose Monitoring, Diabetes Mellitus.*

1. Introduction

Electrical impedance spectroscopy (EIS) is getting more attention day by day as a mean of non-invasive physiological blood glucose monitoring. Although, there are different other means of non-invasive glucose measurement such as optical, photoacoustic and electromagnetic, it is always crucial to select a method that provides deterministic sensitivity of the measuring parameter with respect to the blood glucose variation. This work is aimed to investigate the variation in EIS with respect to the variation of glucose levels in human blood. To characterize this issue, EIS of three different solutions are compared and examined in this work.

Diabetes is one of the major ailments of concern in this 21st century. In 2012, more than 371 million people have diabetes which is increasing all over the world and is predicted to be 380 million by 2025 [1]. Diabetes is not only causing health concern but also have a significant socio-economic impact. In 2012, 4.8 million people died and 471 billion USD were spent due to diabetes [1]. However, the major fact of concern is that around half of the people with diabetes don't know they have it [1] and get diagnosed only when serious condition arises. It may be due to the unavailability of technology, lack of consciousness and the invasive natures of the present diagnosis tools of glucose measurement. But People inherently may show reluctance of using invasive tools for diabetes measurement although having consciousness about the complications of diabetes and it can be predicted easily that if the diabetes can be measured in a non-invasive manner, the rate of using diagnosis tools will be increased which consequently will decrease the no. of undiagnosed people and hence the no. of death by diabetes. Besides, to avoid complexities due to diabetes, frequent glucose monitoring is necessary which is not possible with invasive glucose monitoring devices that requires blood collection at the present state. Moreover, the invasive techniques cause pain, high cost per measurement and potential risk of infection. All these issues inevitably lead to the necessity of a non-invasive glucose measurement system.

Non-invasive methods that are used for the determination of glucose so far can be categorized into two groups. First group includes the methods of near-infrared and mid-infrared absorption, optical rotation, Raman shifts and photo-acoustic absorption where measurements are based on the intrinsic properties of glucose molecules. On the other hand, second group measures the effect of glucose on the physical properties of blood and tissues, includes the methods of electrical impedance, electromagnetic and thermal technology. Among the different non-invasive techniques, infrared (IR) spectroscopy is the most tested and investigated one. [3-5] presents non-invasive glucose monitoring techniques based on IR spectroscopy faces problems cause of low absorption coefficient and non-specific scattering coefficient of glucose in the IR band [2]. Another technique of non-invasive glucose measurement, Raman spectroscopy, on the other hand suffers from the complexity of wavelength instability of laser and

interference by other compounds [2]. Photo-acoustic method is based on the technique to excite the target with a laser and to get the acoustic response [6] heavily sensitive to the temperature and pressure change. On the other hand, [7-10] present electromagnetic sensors for measuring blood glucose are based on the fact that the change in the glucose concentration changes the dielectric parameters of blood. The feasibility of such electromagnetic sensors with in-vitro experiments is presented in [11] where it is shown that the antenna resonant frequency in the range of 1GHz to 10GHz increases when blood glucose increases. The major disadvantage in this method is the change in dielectric property of blood depends on several components other than glucose and will face inaccuracy when it will be tested in-vivo. In contrast, EIS although measures the dielectric property of blood can be improved significantly by proper electrical equivalent circuit modeling. However, the challenge in all these methods is to find a sound and deterministic relation between glucose and non-invasive parameters and to avoid the disturbance by skin-sensor interface and this paper, an experimental investigation of previous work [12], shows EIS as a firm solution in this regard.

The first complete non-invasive glucose monitoring device was approved in 2003 [13] in EU named Pendra by Pendragon Medical Ltd. was based on EIS presented in [14]. The device was based on the measurement of modulus of impedance at resonant frequency (minimum impedance) which was a variable of blood glucose concentration. But when it was in the market for home use, showed less precision as the correlation coefficient was only 0.64 with only 56% data in acceptable range [15]. This is because the resonant frequency can be changed in blood due to elements other than glucose which has not been compensated in Pendra. On the other hand, impedance spectroscopy using voltage-current pulse technique presented in this paper, directly measures the electrical nature of blood where the effect of other elements than blood can be compensated easily using proper circuit modeling.

Voltage and current pulse technique for realizing electrical impedance spectroscopy as a mean of non-invasive blood glucose monitoring are presented in [16, 17] but requires 4 electrodes for current injection and voltage detection. Alternatively, this paper presents a system with only two electrodes for both current injection and voltage detection which would reduce skin irritation due to electrode polarization. In-vitro experiments on three different solutions: 1) 0.9% NaCl, 2) Saline (NaCl 1.3gm, KCl 0.75gm, $Na_3C_6H_5O_7$ 1.45gm, D-glucose 6.75gm in 500mL) and 3) Human Blood are performed and found the linear variation in impedance modulus against different glucose concentrations.

2. Methods and Materials

2.1 Electrical Equivalent Circuit

Biological tissues are generally modeled by similar electrical circuits shown in Fig. 1 [18]. Here, the extracellular medium is modeled by Re which corresponds to the Plasma of blood. Then the cell membrane is modeled by Cm and Rm and the intra-cellular medium is modeled by Ri. In every case, subjected electrical current will flow through biological cells or extra-cellular medium and the current through the cells may be classified as the current across the trans-membrane ionic channel (shown as the path with R_m) or by the plasma membrane (shown as the path with Cm). Due to the very high trans-membrane channel resistance Rm, it may be ignored and the circuit can be simplified with a single extra-cellular medium resistance R_e, an intra-cellular medium resistance R_i and a cell membrane capacitance C_m.

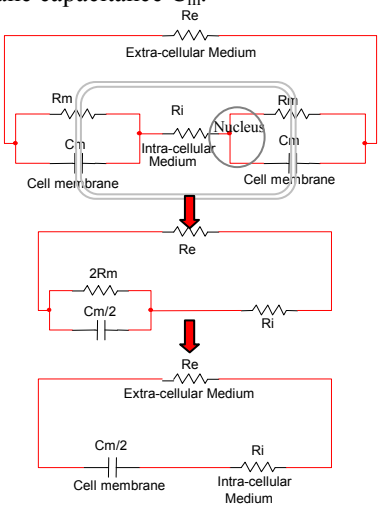

Fig 1. Electrical equivalent circuit of biological cells

When glucose concentration in blood is changed, it changes the ionic balance in the plasma and increases the extra cellular resistance Re. On the other hand, whenever, blood glucose in plasma is increased, water from intra-cellular medium is transferred to the plasma that changes the permittivity of cell membrane Cm and intra-cellular medium resistance Ri. Consequently, the change in blood glucose can be observed by any one parameter of Re, Ri and Cm or collectively by the impedance spectroscopy Z(jw) as shown in Eq. (1). However, the main complexities in blood glucose characterization is due to the change in EIS cause of elements other than glucose. According to Fig. 2 [19], it is evident that, the mostly varied component

in blood is glucose althogh triglycerides (lipid) and urea also vary significantly. But the contribution of lipid is solely in Ri and Cm since it is not soluble in plasma. So, the effect of lipid can be avoided just calculating Re from EIS as presented in [12]. On the other hand, urea is highly soluble and can make significant effect on Re and on EIS. But change in urea is much more lower than change in glucose. So, the glucose variation could be effectively monitored by EIS and the effect of other elements except glucose can also be effectively filtered by observing Re only rather than the measurement based on EIS collectively.

$$Z(jw) = \frac{R_e + jwR_eR_iC_m}{1 + jw(R_e + R_i)C_m} \quad (1)$$

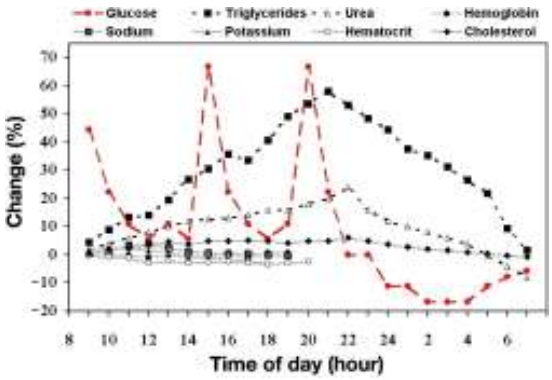

Fig 2. Diurnal blood component variation in blood. Meals are taken around 8:30, 13:30 and 18:30, denoting breakfast, lunch and dinner respectively [19,20].

2.2 Response to Current Pulse and EIS

EIS refers to the presentation of electrical impedance against frequency. One method can be applied for acquiring EIS is current pulse injection and voltage acquisition as shown in Fig. 3. When a current pulse is applied, the voltage developed can be expressed by Eq. (2) where h(t) represents the impulse response of bio-electrical circuit and '*' represents the convolution sum between h(t) and I(t). In this case, the impulse transform H(jw), the Fourier transform of h(t), equals the EIS i.e. Z(jw) which can be obtained by Eq. (3).

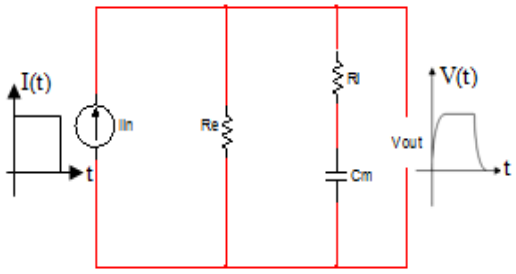

Fig 3. EIS by current injection and voltage detection

$$V(t) = I(t) * h(t) \quad (2)$$

$$H(jw) = \frac{V(jw)}{I(jw)} = Z(jw) \quad (3)$$

Therefore, from experimental data, we can calculate EIS by current pulse injection and voltage detection according to Eq. (3). But these EIS data correspond to the Eq. (1) by which we can estimate different EIS parameters separately that are Re, Ri and Cm [12]. However, this analysis is based on frequency domain and it is also possible to perform a time domain analysis to find out Re, Ri and Cm from estimating rise time, settling time and time constant of voltage response against current pulse. Eq. (4) and (5) represents the input current pulse I(t) and voltage response V(t) of bio-electrical circuit where T represents the duration of current pulse. Eq. (6-8) represent time constant, rise time and settling time respectively and solving these three relations, it is possible to find Re, Ri and Cm. Although, this time domain approach is faster and easier to calculate EIS parameters but erroneous compared to frequency domain analysis requires DFT algorithms to estimate impedance parameters. In this paper, frequency domain analysis is performed for better accuracy.

$$I(t) = u(t) - u(t-T) \quad (4)$$

$$V(t) = u(t)\left[R_e - \frac{R_e^2}{R_e + R_i} e^{-t/(R_e+R_i)C_m}\right] - u(t-T)\left[R_e - \frac{R_e^2}{R_e + R_i} e^{-(t-T)/(R_e+R_i)C_m}\right] \quad (5)$$

$$T_c = (R_e + R_i)C_m \quad (6)$$

$$T_r = 2.2(R_e + R_i)C_m \quad (7)$$

$$T_s = 4(R_e + R_i)C_m \quad (8)$$

Once impedance data is retrieved from frequency domain analysis of voltage and current pulse, it is enough either to work with magnitude or phase of Z(jw) to estimate R_e, R_i and C_m. Eq. (9) and (10) present the magnitude and phase of Z(jw). But Re represents more accurate variation of glucose level compared to Ri and Cm and interestingly Re equals the DC impedance which refers to the $|Z(jw)|$ when w = 0 and can be found easily from Eq. (9).

$$|Z(jw)| = \frac{\sqrt{(R_e + R_eR_i(R_e + R_i)w^2C_m^2)^2 + w^2C_m^2(R_eR_i)^2}}{1 + (R_e + R_i)^2 w^2 C_m^2} \quad (9)$$

$$\theta(w) = -\tan^{-1}\left(\frac{wC_m R_e^2}{1+(R_e+R_i)^2 w^2 C_m^2} \Big/ \frac{R_e + R_e R_i (R_e+R_i) w^2 C^2}{1+(R_e+R_i)^2 w^2 C_m^2} \right) \quad (10)$$

2.3 Materials

Finding and setting up a sound correlation between glucose variation and a non-invasive parameter is crucial always. In this paper, to observe the co-relation between glucose level and EIS, three solutions: 1) 0.9% NaCl, 2) Saline (NaCl 1.3gm, KCl 0.75gm, $Na_3C_6H_5O_7$ 1.45gm, D-glucose 6.75gm in 500mL) and 3) Human Blood are tested. Solutions 1 and 2 are chosen because of their similar behavior with blood although lack cellular components. Since, the DC impedance Re is subjected to non-cellular components of blood, these two solutions are also expected to have similar EIS response against glucose compared to blood at w = 0 which is observed true in experimental results.

3. EIS Measurement System

The operation of EIS measuring system followed in this paper is presented in Fig. 4 basically based on four sections: 1) current injection, 2) voltage acquisition, 3) frequency domain conversion and 4) EIS estimation. The experimental setup of the system is shown in Fig. 5.

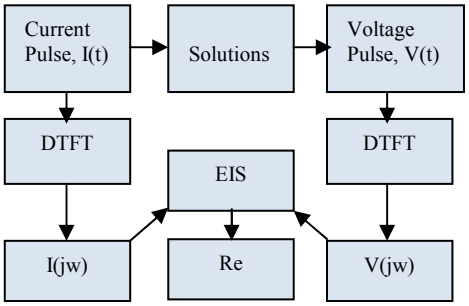

Fig 4. EIS measurement system block diagram

Fig 5. Experimental setup

The major part of the EIS measurement system is the current pulse source generation which is realized in this paper firstly generating a voltage pulse by monostable operation of a 555 timer IC and then converting the voltage pulse to a current pulse using a non-inverting amplifier as shown in Fig. 6 [12]. The input impedance of a 741 IC is 1MΩ and until the impedance of load exceeds 10kΩ the circuit in Fig. 6 will act as an ideal current source which is enough impedance range for human blood normally lies below 1kΩ.

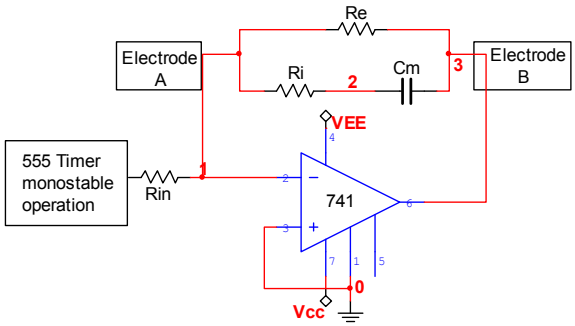

Fig 6. Current pulse generation

One of the major advantages of the system presented here for EIS measurement is using only two electrodes instead of four. The two electrode positions are shown in Fig. 6 as Electrode A and Electrode B. The parallel network of Re, Ri and Cm represent the solutions. In this work, the solutions are taken into a rectangular box of dimensions $2'' \times 2'' \times 2''$ where two sides are used as Electrode A and Electrode B made of Cu. D-glucose is added to manually vary the glucose concentration of solutions. The voltage across the solution is acquired using Agilent InfiniiVision 7000B Series oscilloscope and Matlab R2011a Instrument Control Toolbox after an instrumentation amplifier in Fig. 7 for noise rejection as shown in Fig. 8. The gain can also be possible to control by this instrumentation amplifier according to $A_{CL} = 1 + 2R / R_g$. Once voltage data are acquired, the EIS is estimated using Discrete Time Fourier Transform.

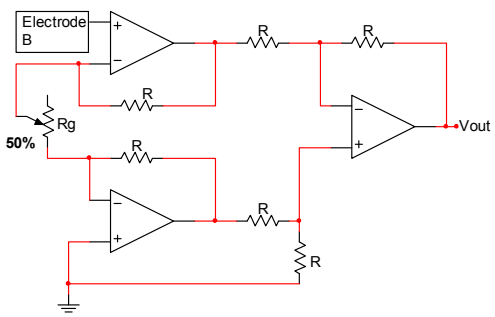

Fig 7. Instrumentation amplifier

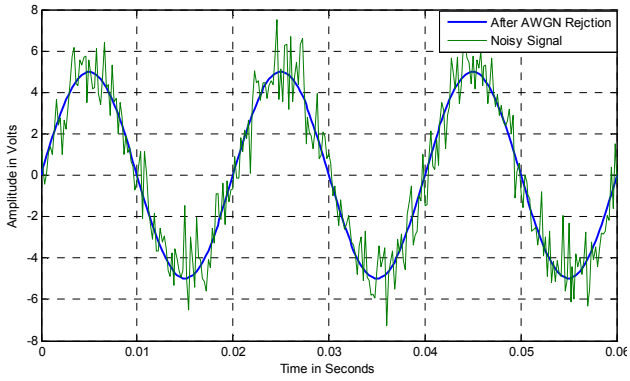

Fig 8. Noise rejection by instrumentation amplifier

4. Results and Discussions

EIS of three solutions: 1) 0.9% NaCl, 2) Saline and 3) Human blood is estimated against glucose variation every 25mg/dl. After taking every reading by applying a current pulse, the solutions are kept around 15-20 minutes to be relaxed. Fig. 9 shows the EIS variation of 0.9% NaCl solution. It is evident that EIS has the significant change for every 25mg/dl change in glucose concentration. Moreover, the DC impedance that is the value of EIS when w=0 encircled in Fig. 9 shows almost linear variation.

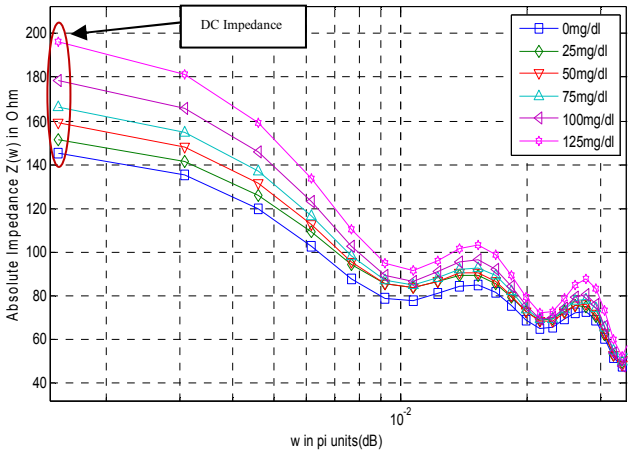

Fig 9. EIS of 0.9% NaCl solution

Again, Fig. 10 shows the variation in EIS for saline and linear variation in DC impedance is found here too. However, for the glucose variation of 0-125mg/dl, the DC impedance varies from about 140 to 200Ω in NaCl solution which is just 180-200Ω in saline for 0-225mg/dl glucose variation. That indicates the change in DC impedance is larger in 0.9% NaCl solution than saline. However, both solutions indicates the firm relation between glucose variation and EIS.

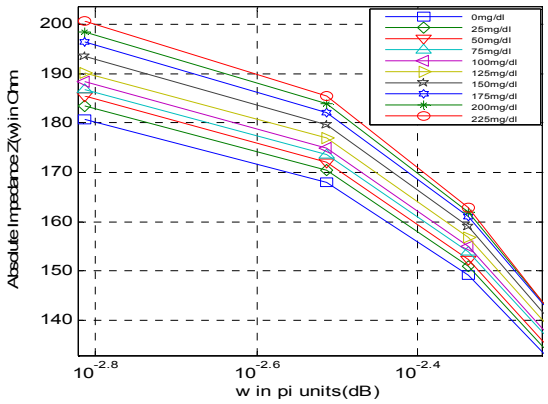

Fig 10. EIS variation of saline

Fig, 11-13 show the variation in EIS for three human blood samples for change in glucose concentration of every 25mg/dl. It is clear from three sample data that, when glucose concentration increases, the impedance of blood also increases. Moreover, the DC impedances of three blood samples also get changed linearly when glucose concentration varies as it was in saline and NaCl solution. However, the rate of change in DC impedance is not equal for three blood samples. For blood sample 1, although the DC impedance varies from around 200-295Ω for 0-250mg/dl change in gluocose concentration, it is around 325-360Ω for 0-125mg/dl for blood sample 2 and 320-345Ω for 0-250mg/dl. It is because of the variation of nature and ingredients in blood samples. For example, if the blood sample 1 has the lower amount of ionic compounds than blood sample 2 and 3, its impedance will be affected more by the variation of glucose concentration. Another factor may be the variation of blood cells in different samples. However, for a particular blood sample, EIS changes linearly in change of glucose concentration and sample specific callibration could be useful for glucose measurement from EIS.

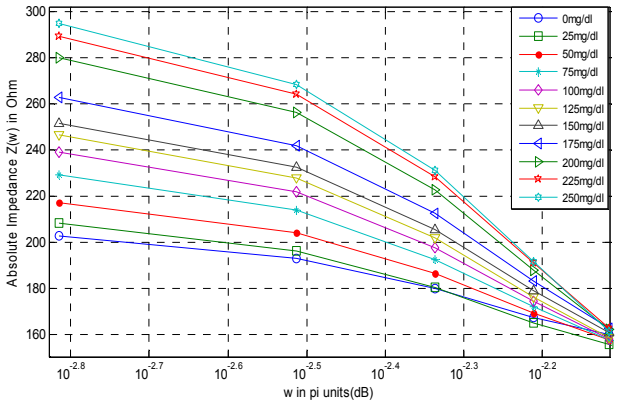

Fig 11. EIS variation in blood sample 1

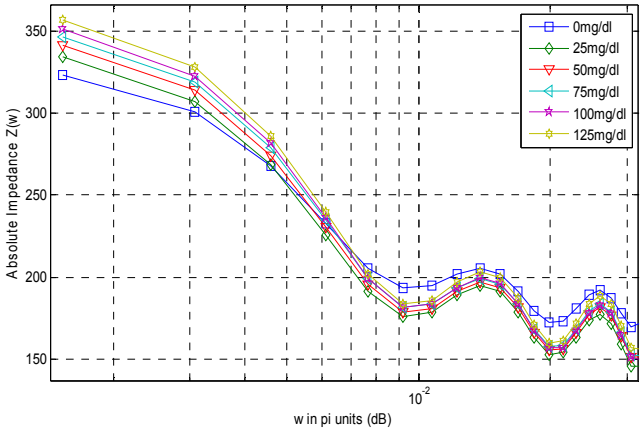

Fig 12: EIS variation in blood sample 2

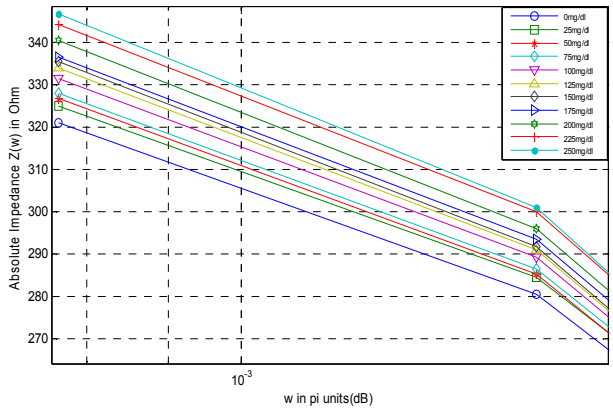

Fig 13. EIS variation of blood sample 3

5. Conclusion

Finding a sound correlation between blood glucose concentration and a non-invasive parameter is challenging always. This work measures EIS against different blood glucose concentration and found strong correlation between DC impedance of EIS and glucose concentrations. EIS increases linearly when glucose concentration increases. Although, EIS in different blood samples show different rate of change, initial calibration can be used to cope up this situation. Finally, glucose concentration in human blood can be measured accurately by EIS and since no blood collection or invasion would require in this method when tested in-vivo, non-invasive and continuous blood glucose monitoring would be possible accurately. Disturbances due to electrode-skin interference, skin and muscle characteristics can also be eliminated effectively using EIS when only DC impedance is get considered.

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References

[1] "The fifth edition of the IDF diabetes atlas", International Diabetes Federation, 2012.

[2] A. Tura, A. Maran and G. Pacini, "Non-invasive glucose monitoring: Assessment of technologies and devices according to quantitative criteria", Diabetes Research and Clinical Practice, vol. 77, pp.16-40, 2007.

[3] T. MoriKawa, F. Saiki, H. Ishizawa and E. Toba, "Non-invasive measurement of blood glucose based on optical sensing and internal standard method", IEEE Int. Joint Conf. on SICE-ICASE, pp. 1481-1484, Oct. 2006.

[4] H. Ishizawa, A. Muro, T. Takano, K. Honda and H. Kanai, "Non-invasive blood glucose measurement based on ATR infrared spectroscopy", Annual Conf. on SICE, pp. 321-324, Aug., 2008.

[5] S. Koyama, Y. Miyauchi, T. Horiguchi and H. Ishizawa, "Non-invasive measurement of blood glucose of diabetic based on IR spectroscopy", Annual Conf. of SICE, pp. 3425-3426, 2010.

[6] O. C. Kulkarni, P. Mandal, S. S. Das and S. Banerjee, "A feasibility study on non-invasive blood glucose measurement using photoacoustic method", IEEE Int. Conf. on Bioinformatics and Biomedical Engineering, pp. 1-4, 2010.

[7] B. R. Jean, E. C. Green and M. J. McClung, "A microwave frequency sensor for non-invasive blood-glucose measurement", IEEE Sensors Applications Symposium, pp. 4-7, 2008.

[8] M. Hofmann, T Fersch, R. Weigel, G. Fischer and D. Kissinger, "A novel approach to non-invasive blood glucose measurement based on RF transmission", IEEE Int. Workshop on Medical Measurements and Applications, pp. 39-42, 2011.

[9] V. V. Meriakri, E. E. Chigrai, I. P. Nikitin and M. P. Parkhomenko, "Dielectric properties of water solution with small content of glucose in the millimeter wave band and the determination of glucose in blood", 6th Int. Symp. On Physics and Engineering of Microwaves, Millimeter and Submillimeter Waves, pp. 873-875, 2007.

[10] Y. Nikawa and D. Someya, "Non-invasive measurement of blood sugar level by millimeter waves", IEEE MTT-S Int. Microwave Symp. Digest, pp. 171-174, 2001.

[11] J. Venkataraman and B. Freer, "Feasibility of non-invasive blood glucose monitoring", IEEE Int. Symp. on Antenna and Propagation, pp. 603-606, 2011.

[12] S. K. Dhar and Q. D. Hossain, "Non-invasive bio-impedance measurement using voltage-current pulse technique", Int. Conf. on Electrical, Electronics and Biomedical Engineering, pp-70-74, May, 2012.

[13]"Unsafe and ineffective devices approved in the EU that were not approved in the US", US Department of Health and Human Services, May 2012.

[14] A. Caduff, E. Hirt, Yu. Feldman, Z. Ali and L. Heinemann, "First human experiments with a novel non-invasive, non-optical continuous glucose monitoring system", Journal of Biosensors and Bioelectronics, vol. 19, issue 3, pp. 209-217, Nov., 2003.

[15] C. M. Girardin, C. Huot, M. Gonthier and E. Delvin, "Continuous glucose monitoring: A review of biochemical perspectives and clinical use in type 1 diabetes", Journal of Clinical Biochemistry, vol. 42, issue 3, pp. 136-142, 2009.

[16] A. M. Aguilar and R. P. Areny, "Electrical impedance measurement using voltage/current pulse excitation", 19th IMEKO World Congress on Fundamental and Applied Metrology, pp. 662-667, Sept. 2009.

[17] T. Dai and A. Adler, "In vivo blood characterization from bioimpedance spectroscopy of blood pooling", IEEE Transaction on Instrumentation and Measurement, vol. 58, no. 11, Nov. 2009.

[18] L. I. Kalakutskiy and S. A. Akulov, "Modeling of the bioelectrical impedance of blood by synthesis of the equivalent electrical circuits," Proc. IFMBE 25/VII, pp. 575-577, 2009.

[19] SJ Pocock, D. Ashby, AG Shper, M Walker, G. Broughton, "Diurnal variations in serum biochemical and haematological measurements", Journal of Clinical Pathology, vol.42, no.2, pp-172-179, Feb. 1989.

[20] I. H. Boehm, A. Gal, A. M. Raykhaman, J. D. Zahn, E. Naidis and Y. Mayzel, "Non-invasive glucose monitoring: a novel approach", Journal of Diabetes Science and Technology, vol.3, issue 2, March 2009.

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