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NIVA_B – Non-Invasive Determination of Blood Glucose

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Abstract

NIVA_B is a TROUT GmbH medical technology project on non-invasive determination of blood glucose. The NIVA_B objective is to provide an easy-to-use non-invasive blood glucose measurement system for continuous and pain-free detection of blood glucose values. The system is based on impedance spectroscopy and uses an artificial neural network to calculate the individual correlation between impedance values and blood glucose level. NIVA_B generates a glucose value every minute. A series of pre-clinical tests have shown very promising results. There is no need to take blood samples, except for a tiny drop for calibration, and this non-invasive approach reduces the risk of infection to a minimum. A patent was granted by the European Patent Office in 2014 - EP 2196140.

Key words: non-invasive, blood glucose, self-control, wearable, artificial neural network

Motivation

According to the IDF Diabetes Atlas [1], 285 million people are currently affected by diabetes mellitus throughout the world - with 55 million in Europe alone. By 2030, the IDF predicts 438 million diabetes cases worldwide, and about 66 million cases in Europe. These numbers indicate the huge demand for a non-invasive glucose measurement system, as all persons affected by diabetes are required to monitor and control their glucose levels. The disease can only be managed if the blood glucose level is determined several times a day. There are various invasive measurement devices which determine glucose levels using a small sample of blood. Patients have to lance a finger to obtain the required sample. The blood is then applied to the measurement process using a carrier (glucose test strip). Afterwards the blood glucose level is determined by chemical methods (glucose oxidase).

Our non-invasive approach avoids this pain and risk of infection. The next step is to integrate the components of the system into a miniaturized, Internet-enabled system. Potential applications include glucose self-monitoring, clinical environment and overnight data acquisition.

Methodology

The measuring system NIVA_B uses a process for the non-invasive determination of blood glucose level (in mg/dl or mmol/l) in human blood by measuring the impedance in a part of the patient's body. The calculation module notes a change in blood glucose level. The coefficients of the approximation function are determined with reference data taken invasively. By administering HF and LF current to the patient's body, the measurement of the HF and LF impedances and the input of these results into an artificial neural network lead to a blood glucose level. HF charge is between 1-9 MHz; the LF charge between 10-100 kHz.

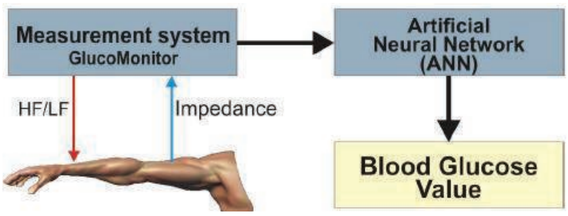

Fig. 1. Overview

The frequency dictates the depth of subcutaneous tissue where impedance is determined. [5]

Earlier concepts for non-invasive determination of blood glucose attempted to take measurements directly in the blood. For the past couple of years, however, the glucose level has been measured in the sub-skin fatty tissue, as the glucose concentration here corresponds to that in the blood (with a certain delay).

The non-invasive determination of blood glucose is performed with impedance spectroscopy by using the correlation between

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glucose and tissue conductance in relation to impedance. So the physiological model of the NIVA_B system uses the dependency f=G(Z) between the glucose level G and the impedances Z. [2][3]

The effect of changing glucose concentration on the impedance under the skin depends on the reaction of the individual organism to the change of the osmotic properties of the interstitial liquid. It alters its volume V and thus the volume of the cells and density of their membranes and also the conductivity C of ionic particles. [4]

It is known that the blood glucose level correlates with the impedance Z. The relation between blood glucose G and impedance Z is as follows:

$$G = f(Z) : \Delta G \Rightarrow \Delta V_{out} \Rightarrow \Delta C \Rightarrow \Delta Z$$

The level of blood glucose influences the osmotic pressure and therefore the conductivity of the tissue. Increased blood glucose level means increased osmotic pressure. This means that the size of the cells is reduced while the volume of liquid V_{out} actually increases, leading to a greater distance between individual cells which in turn means that the conductivity C increases and therefore the impedance Z decreases. This means that with increasing blood glucose levels the extra cellular liquid volume V_{out} increases as a result of osmotic processes. I.e. when the blood glucose level increases, the osmotic pressure also rises, causing the cells to become smaller. Smaller cells mean a greater extra cellular volume which leads to an increase in conductivity.

However, the context described may vary individually. Therefor an individually parametrized artificial neural network is applied in order to get correct results.

Furthermore the following applies to the correlation between impedance and liquid volumes:

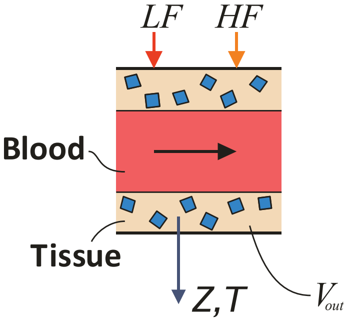

Fig. 2. Overview of the measurement setup

By introduction of a high-frequency charge, the impedance is determined in the total liquid amount. The total amount of liquid is $V_{tot} = V_{in} + V_{out}$ (V_{in} = liquid volume in the cell; V_{out} = liquid volume outside the cell. With introduction of a low-frequency charge into the object, the impedance can be represented with just the liquid volume outside the cells.

The dependent relationship between impedance Z and the liquid volume in the tissue is as follows:

$$Z = \mathrm{f}\,(\mathrm{V}) \begin{cases} Z \sim \dfrac{1}{C^{LF}} \sim \dfrac{1}{V_{out}} \\ Z \sim \dfrac{1}{C^{HF}} \sim \dfrac{1}{V_{in}} \end{cases}$$

That means, for the LF-part, the impedance acts inversely proportional to the low-frequency conductivity and thus, inversely proportional to the extra cellular liquid volume V_{out}. For the HF-part, the impedance acts inversely proportional to the high-frequency conductivity C and thus inversely proportional to the sum V_{tot} of the intercellular liquid volume V_{in} and the extra cellular liquid volume V_{out}.

It should be mentioned that the correlation between blood glucose and impedance cannot be represented by a describable and definite algorithm and also varies from patient to patient and environmentally.

Thus, the use of an artificial neuronal network to display non-linear functions, which is continuously affected by subjective parameters, was advisable.

One advantage of an artificial neuronal network, particularly a calibrated artificial neuronal network, is that the whole procedure becomes more and more precise, depending on the frequency of measurements and particularly the frequency of calibrations. This means that the procedure adapts itself optimally to a specific patient in the course of time, because a neuronal network is adaptive axiomatically. The accuracy of the procedure is increased by taking the skin temperature into account.

When measuring the impedance, it is also taken into account how moist or dry the patient's skin is. It is known that the dryer the surface of the skin, the higher the electric resistance. The contact influence through the moistness is compensated by using a second pair of electrodes. The approach of a 4 point measurement is realized by the applied sensor and compensates the effect of contact resistance.

System Requirements

NIVA_B has been developed according to the following requirements:

- ✓ Development of a system for continuous, non-invasive determination of glucose levels for humans and corresponding functions for use in performance evaluation.
- ✓ Data recording integrated in measurement device.
- ✓ Functions for displaying and monitoring the state of charge.
- ✓ Retrospective calculation of blood glucose levels
- ✓ 24h of operation time (sufficient storage and battery)
- ✓ Compliant material for wristband
- ✓ Flexible, skin-friendly wristband; adjustable to fit different arm sizes
- ✓ Standard interface to PC for data transfer (USB)
- ✓ Preferably integrated device with wristband/measurement in one system
- ✓ Evaluation by PC after data acquisition

System Components

Figure 3 shows the components of the system: the measuring device for data acquisition SYS01, the sensor for the impedance measurement SYS 02 and a laptop computer SYS03 running the artificial neural network, in order to calculate glucose values from the impedance spectra.

Fig. 3. System Components

Measuring Device

Figure 4 shows the device in data acquisition (measuring) mode. The first two lines (LOW / HIGH) include three numbers. The first two numbers indicate the measured ADC values from the skin voltage and the flowing current. The last one is the calculated skin impedance for the frequency. The third line (TEMP) comprises the measured skin surface temperature. The fourth line (VOLT) shows the measured voltage from the accumulator and a graphical representation of a charge indicator. The fifth line (DATA) indicates the bytes saved in the data flash. And finally, date and time.

Fig. 4. Device for Data Acquisition

Sensor

Four titanium electrodes on a wristlet made from teflon are used for a self-calibrating 4-point impedance measurement, optimized at two frequencies.

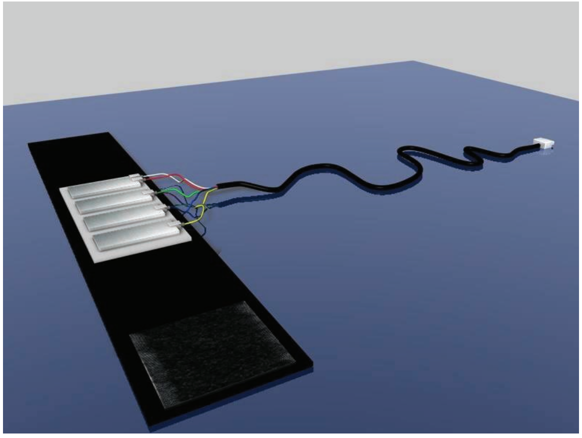

Fig. 5. Sensor

Artificial Neural Network ANN

Neural networks are pattern recognition systems inspired by the functionality of biological neural networks. One of the most important neural systems is the human brain. The nervous system consists of biologically independent neurons which are connected by synapses. Each neuron is connected to thousands of other neurons. By transmitting impulses, the synapses pass information between the neurons. Each impulse causes a reaction. In the learning process, the synapses between the neurons are modified. The reaction to an impulse is adjusted by trial and error until the feedback is optimal and recurring patterns can be recognized.

Artificial neural networks simulate this way of learning and transmitting information. Due to the limited calculation power of a computer system far less neurons with a dedicated number of connections are used.

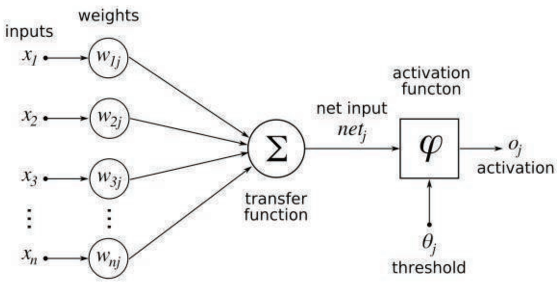

Fig. 6. Neuron in an Artificial Neural Network ANN

An artificial neural net or network is made up of neurons, organised in layers and connected to each other through synapses. Every neural net has a certain number of input neurons and an output layer, containing the output neurons. Furthermore, an ANN typically has at least one hidden layer. The input neurons receive the data and feed it into the neuronal net. The data runs through the neurons of all layers and is thereby processed. Eventually, the output neurons hand out the calculated results.

In detail, the transformation of the data at the pass-through of the different layers is carried out as follows: a neuron recieves data, either input data into the neuronal net or in a processed state from neurons of the previous layer. All data is then weighted and added. A marginal value is substracted from the sum, and the result is used to calculate the value that the neuron will pass on, using the 'Tan-Sigmoid-Function' transfer function.

$$T(n) = \frac{2}{1+e^{(-2n)}} - 1$$

It is used advantageously as transfer function in the hidden neurons. Both the input neurons and the neurons in the output layer use the identity function T(n) = n.

The artificial neural networks for NIVA_B is designed to contain two hidden layers, where the first hidden layer contains five neurons, the second three and the output layer one neuron. However, the number of neurons in a neuronal network is not limited axiomatically.

The artificial neural network allows the results to become more and more precise during the course of a conducted measuring. This means that the neural net is adaptive autonomously. For the precision of the results, specifically the level of blood glucose, the value assignment of the weights and the marginal values is the deciding factor. The marginal values and the weights inside the neural net are initially allocated with randomly chosen, arbitrary values.

For training, the net is then fed with data, i.e. impedances and temperature values and the according results (level of blood glucose). The net calculates a value from the given data and compares it to the invasively determined level of blood glucose. According to the occurring variations, the marginal values and the weights in the network are adjusted. This takes place using numerical procedures, e.g. the Levenberg-Marquard-Algorithm. This neural net learning procedure is repeated until the variation does not exceed a desired value.

In order to improve the calculation result, nine ANNs are used at the same time, while the two networks showing the highest sum of error squares are dropped. The average result of the

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remaining seven is the glucose level output of the system.

Study

Number of participants: 32, number of useful data: 20, amount of data 2000 minutes per participant. Three days training of the ANN, two days comparison of actual value and desired value.

Fig. 8. Patient with sensor and data recorder

Data Processing

Example:

Figure 9 shows the data directly from the sensor (raw data) and pre-evaluated on the measurement device (filtered). In order to train the ANN an invasive collection of data is taken simultaneously (reference data, in figure 13 again). The horizontal axis shows the time in minutes, the vertical relative units.

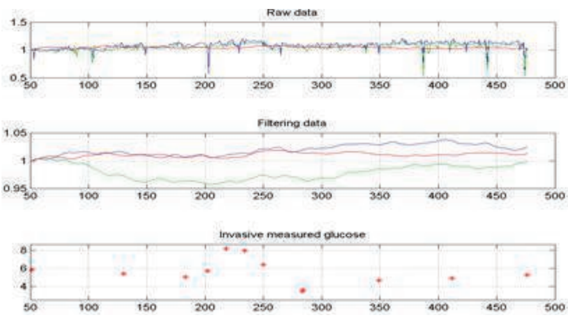

Fig. 9. Raw data, filtered data and reference data

The predictors in figure 10 represent the values of the input neurons after normalization.

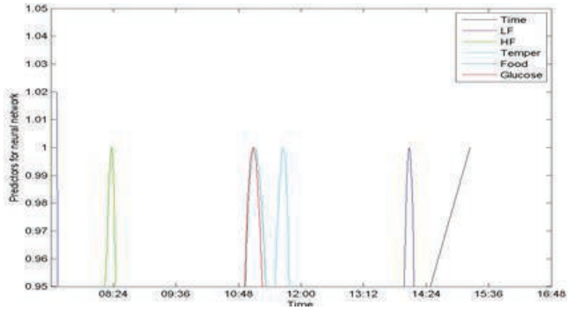

Fig. 10. Normalized Predictors

Figure 11 shows the relation of the weight factors of the different input neurons. [6]

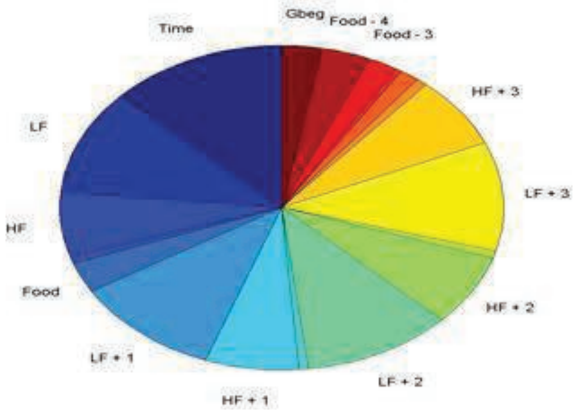

Fig. 11. Pie Chart for the Weight Factors

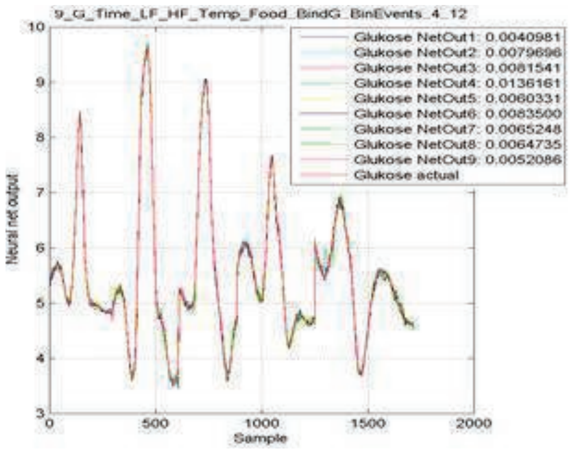

Fig. 12. Calculation Results of Nine Nets

An average of the seven best net results provides a glucose graph for the individual.

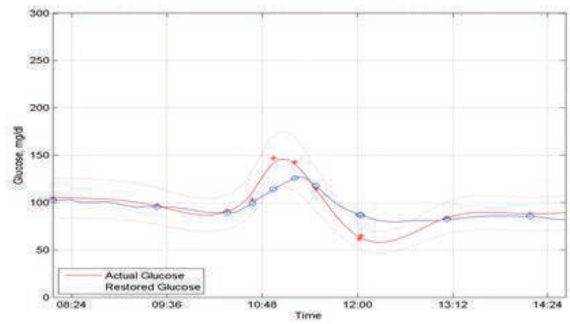

Fig. 13. Glucose Graph

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A Clarke Error Grid shows calculated glucose values by the ANN in relation to reference data taken from a proved invasive system. Entries should be close to the bisecting line or in section A or, at minimum, in section B.

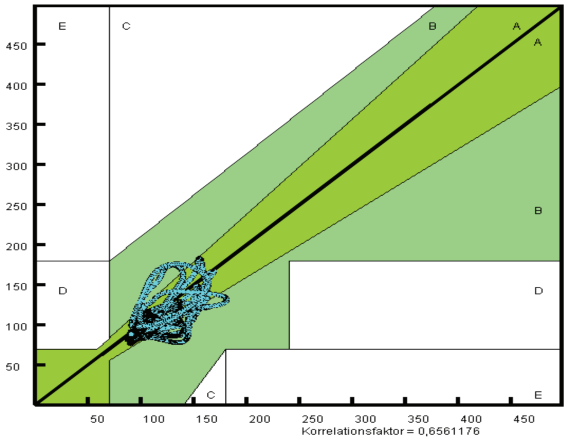

Fig. 14. Clark Error Diagram

Further Developments

The glucose values are calculated by the measurement unit. There's a wireless transfer of these values to the display device which may be a smartphone or smartwatch. The display unit includes controls for recording of events such as food and insulin ingestion. Additionally, the display device provides functions, e.g. for data history or data transfer to the internet.

Fig. 15. DesignStudy

Basic functions:

1. Info page including
    a. Hospitals (availability and Address)
    b. Doctors, specialists
    c. Ophthalmologists
    d. Podiatrists
    e. The orthopedic shoemaker
2. Navigation
    a. To addresses on the info page
    b. To additional addresses
3. Emergency
    a. Emergency call
    b. Emergency drugs
    c. People to notify
4. Calendar with reminder
    a. Meals
    b. Measurement of blood sugar
    c. HB1C laboratory control according to health card
    d. Measuring blood pressure
    e. Insulin administration
    f. Drugs
    g. Dates
5. Guides
    a. BE Calculator
    b. Calories burned calculator
    c. Suggestions for diets
    d. Sport (which sport causes what)
    e. Pedicure
6. Diary
    a. Blood sugar levels data & time
    b. Blood pressure values
    c. Voice notes
    d. Text notes
    e. Photos, videos

Advanced Features:

1. Interaction with speech input and speech output
2. Transfer of blood glucose level to any other invasive systems
3. Auto Tune the calendar with, for example, Outlook
4. Preparation for operation and data communication for NIVA_B
5. Evaluation of the graphic (blood glucose levels over time - steep climbs and descents)
6. Possibility of automatic communication of the data, if cleared by the user

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