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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Glucose concentration monitoring using near-infrared spectrum of spent dialysis fluid in hemodialysis patients

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SUMMARY

Introduction/Objective Diabetic nephropathy leading to end-stage renal disease is a major health problem worldwide. Hemodialysis (HD) treatment is associated with glycemia variations. Diabetic patients on HD might benefit from a non-invasive online glycemia monitoring system.

The aim of this study was to assess the glucose concentration from the matrix of the spent dialysate fluid using near-infrared (NIR) spectroscopy.

Methods Blood samples and spent dialysate were collected in the 15th minute of the HD treatment from 15 patients. The spent dialysis fluid was characterized by a NIR spectrometer in the range of 900–1300 nm. In order to apply the artificial neural network (ANN) and train it, the MATLAB NFTOOL program was used. The testing and training of the ANN were executed using the NIR spectrum of the spent dialysis fluid as input, and the glucose concentration as output.

Results A significant correlation in excess of 93% between the NIR spectrum of the spent dialysate and the blood glucose concentration (3–9 mmol/l) was found.

Conclusions NIR spectroscopy is a non-invasive and reliable method of glycemia monitoring which can be used in maintaining HD patients.

Keywords: hemodialysis; machine learning; spent dialysate; VIS-NIR; patient-specific

INTRODUCTION

Chronic kidney disease and diabetes mellitus are public health problems that influence millions of people all over the world. The latest estimates from the International Diabetes Federation suggest that there were 415 million diabetes mellitus patients in 2015 and that there will be 642 million by 2040 [1]. Inadequate blood glucose control is considered the major cause of diabetic nephropathy and the progression of renal insufficiency, eventually leading to end-stage renal disease requiring renal replacement treatments – either transplantation or dialysis.

The most-studied biological fluids of clinical interest are blood, urine, and, recently, spent dialysate. The dialysis fluid is obtained by mixing water for dialysis with an electrolyte concentrate in a dialysis machine. This machine guarantees the electrolytic composition, the pH, temperature, and the flow rate of the dialysis liquid. Heise et al. [2] gave a complete overview of biological fluids that can be explored using the near-infrared (NIR) spectroscopy. Eddy and Arnold [3] have shown the possibility of glucose detection using NIR spectroscopy.

Hemodialysis (HD) patients with diabetes mellitus must undergo frequent controls of glycemia. Standard monitoring methods are uncomfortable, invasive, and painful. In addition, they only give the interstitial glucose level. Furthermore, it has been shown that the blood glucose levels vary during the HD treatment. During the procedure, the glycemia tends to decrease, while it increases when the HD session ends. Thus, at least for HD diabetic patients, a non-invasive, painless, on-line glycemia monitoring would be beneficial as both hypo- and hyperglycemia should be avoided [4].

However, on-line monitoring of suppressants such as urea, creatinine or blood glucose is complicated by the fact that blood is a highly saturated fluid, prone to clotting [5, 6]. Monitoring of the glucose in the spent dialysate makes the system more flexible. An optical sensor, which simply shines a beam of light through a fluid that contains glucose and uses the principle that the absorption pattern of near-infrared light can be quantitatively related to the glucose concentration may be a simple but effective solution.

Glycemic patterns are still hardly predictable, making it difficult to control blood glucose levels without a risk of hypoglycemia. It is important for clinicians to be aware that there are limitations of specific point-of-care glucose meters [7]. Different assays are used for the quantification of glucose; one of the most sophisticated methods is infrared spectroscopy.

Non-invasive methods for monitoring glucose level based on infrared spectroscopy were first invented during the 1990s [8]. Since then, a wide range of techniques has been developed

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for the non-invasive observation of glucose based on chemical, optical, and electrochemical techniques [9–12].

This development of non-invasive techniques was preceded by successful *in vitro* studies that were based on the determination of glucose in aqueous solutions, or whole blood by NIRS [13, 14, 15]. Studies were mainly based on the effects of glucose on certain secondary processes. One of the most famous examples is effect of glucose on the scattering properties of tissue. However, propagation of light through tissue is complicated by the heterogeneous nature of the tissue matrix, thus creating a problem [13].

To the best of our knowledge, there is no published work on automatic glucose level anomaly detection based on characterization by ultraviolet–visible–near-infrared spectroscopy (UV–VIS–NIR) of the spent dialysate.

METHODS

During the research, patients without diabetes were selected because they have insignificant blood glucose fluctuations. The goal was to detect even the smallest changes in glucose concentration. It is expected that the machine learning algorithm would detect greater changes in concentrations with greater accuracy. The maximum value of glucose recorded during the research was 15.7 mmol/l, which is outside the range of normal values in the blood, while the minimum value was 3.9 mmol/l. The study included 15 non-diabetic male patients with end-stage renal disease on HD. All HD treatments were performed under the standard protocol, including ultrafiltration rates prescribed to remove the interdialytic weight gain. Dialysis was performed using Dialog+ Adimea (B. Braun Avitum AG, Melsungen, Germany) machines. The dialysate contained Na^+ 138 mmol/L, Cl^- 110.5 mmol/l, K^+ 2 mmol/l, Ca^{++} 1.75 mmol/l or 1.5 mmol/l, Mg^{++} 1 mmol/l, CH_3COO^- 3 mmol/l, HCO_3^- 32 mmol/l, glucose 1 g/l. The mean dialysate flow was 500 ml/minute, and mean effective blood flow was 300 ml/minute. All the patients were dialyzed via arterio–venous fistulas using a two-needle system. The Ethics Committee of the Dr Dragiša Mišović – Dedinje University Hospital Center, where the study was performed, reviewed the study protocols and all patients provided an informed consent before participating.

Sample collection

Samples of spent dialysate were collected directly from the dialyzer outlet, 15 minutes after the beginning of the dialysis procedure. At the same time, blood samples were taken from the arterial blood line, before entering the dialysis circuit. For each sample, 15 ml of spent dialysate solution was collected into a container and stored at room temperature for approximately three hours before being transported to the research laboratory.

Sample analysis

Blood glucose was measured using the Dimension R×L Max (Siemens Healthcare GmbH, Erlangen, Germany) machine. The assay is based on the hexokinase method. VIS-NIR absorbance spectra of the samples were measured the day after the HD treatment. The absorption spectrum of each sample was measured three times. UV–VIS–NIR optical absorption spectra have been registered using the spectrometer Lambda 950 (Perkin Elmer, Waltham, MA, USA). The wavelength region of interest was 900–1300 nm, and the UV/VIS resolution was set to 2 nm. The instrument was connected to a PC running the Windows 7 operating system and was controlled by the Perkin Elmer UV WIN LAB Explorer. Serum glucose was measured using the Dimension RxLMax (Siemens Healthcare GmbH) machine. The assay is based on the hexokinase method. Glucose level above 6 mmol/L was considered hyperglycemic [16].

Machine learning methods

Here, in order to form the artificial neural network (ANN) and its training, the NFTOOL of MATLAB (The MathWorks, Inc., Natick, MA, USA) program was used. The neural network used for function fitting was a two-layer feedforward network, with a sigmoid transfer function in the hidden layer and a linear transfer function in the output layer.

The test set data have no effect on the training process and it provides an independent measure of network performance during and after training. The training starts with two and finishes with 1000 hidden neurons. The hidden-layer neurons are increased when network is not performing well. The optimum number of hidden layers was determined to be four. Training multiple times generates different results due to different initialization of connection weights and different initial condition.

The NIR spectrum of spent dialysis fluid is used as inputs and red blood parameters was taken as output. The NIR spectrum of the spent dialysis fluid was used as the input to the network, and the blood glucose concentration as the output. In the network, Bayesian regularization function is used for network training.

RESULTS

The best results were achieved using four hidden neurons. The Bayesian regularization algorithm was used for the training of the network. With these settings, the input vectors and target vectors were randomly divided into training (207 samples) and test (90 samples) sets.

The following regression plot displays the network outputs with respect to targets for training and test sets. If $R^2 = 1$, this indicates that there is an exact linear relationship between outputs and targets. If R^2 is close to zero, then there is no linear relationship between the outputs and targets. The correlation coefficient (R-value) measures the correlation between outputs and targets. The correlation was considered excellent if R^2 was > 0.95, very good if R^2 was > 0.9 and < 0.95, good if R^2 was > 0.6 and < 0.8, and poor if R^2 was < 0.6.

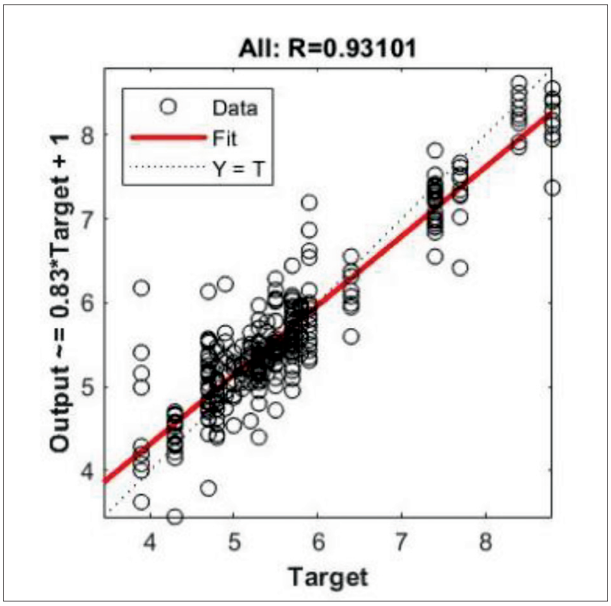

Figure 1. Regression plot between the near-infrared absorbance of spent dialysate and the glucose concentration in the patient blood during a hemodialysis session

Figure 1 shows the regression plot between the NIR-absorbance of spent dialysate and the glucose concentration in the patient blood during an HD session (wavelength range 900–1300 nm, R^2 training = 0.96, R^2 test = 0.67, R^2 all = 0.93, number of spectra used for training was N = 270). The average glucose concentration in patients' blood was 5.72 ± 1.61 mmol/l. A good correlation of these data with the glucose levels in the patients' blood was confirmed by the analysis of discrete blood samples taken from arterial lines.

Figure 2 represents a plot of the train and test mean squared errors (MSE) with epochs. The best train performance was achieved at the epoch 1000, with the smallest MSE of 0.1131. The best test parameters were achieved at epoch 100. The equation relating the predicted and measured values is Output = 0.83 × Target + 1.

Figure 3 shows the distribution of the train and test errors for the trained network.

DISCUSSION

The prevalence of diabetes mellitus complications can be attenuated by adequate glycemic control pertinent to frequent blood glucose monitoring. Unfortunately, most of the available glucose measurement devices are invasive, making the procedure, which has to be repeated several times per day rather uncomfortable and painful. Besides this discomfort, diabetic patients on HD further undergo painful vein punctures every few days for dialysis treatment. Furthermore, there is evidence that HD treatment is associated with intradialytic hypoglycemia and postdialytic hyperglycemia [17]. Therefore, these patients would greatly benefit from a non-invasive intradialytic glucose monitoring.

NIR spectroscopy can be used as an alternative, non-invasive method for clinical analyses. In this method, NIR light is transmitted through or absorbed by the sample, and the substance concentration is predicted by analysis of the transmitted spectral information. Information about complex substances can be obtained from a single NIR spectrum [18]. Data obtained from the NIR spectrum of the spent dialysate fluid can be used for on-line monitoring of blood glucose concentration. The principle that the absorption pattern of NIR light can be quantitatively related to the glucose concentration has been confirmed in a number of previous studies [18–21].

Among all the available methods, the PLS regression has been used most widely for the analysis of NIR spectral data [18, 22]. The biggest problem with PLS methods is that the spectrum property relationship is supposed to be linear. However, this premise cannot be applied to systems with strong intermolecular or intramolecular interactions. If one measures the amount of glucose in a fluid that contains other substituents, the Beer–Lambert law cannot be applied because of interactions between components, an incorrect distribution of fluid components, and a baseline shift. All of these lead to a nonlinear system. This makes

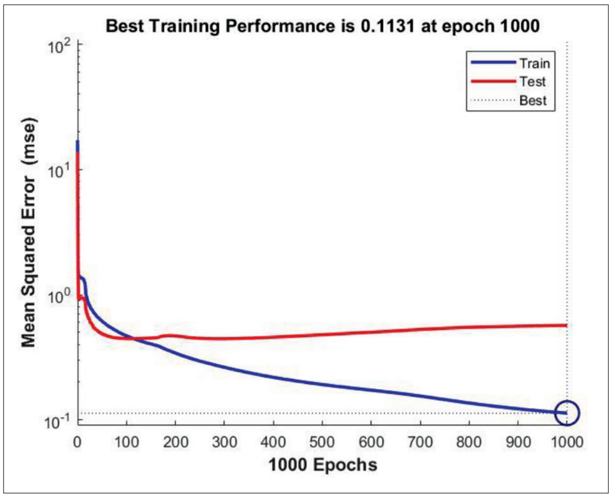

Figure 2. Train–performance plot: the mean squared error of the train and test data is shown against the training iteration number (epoch)

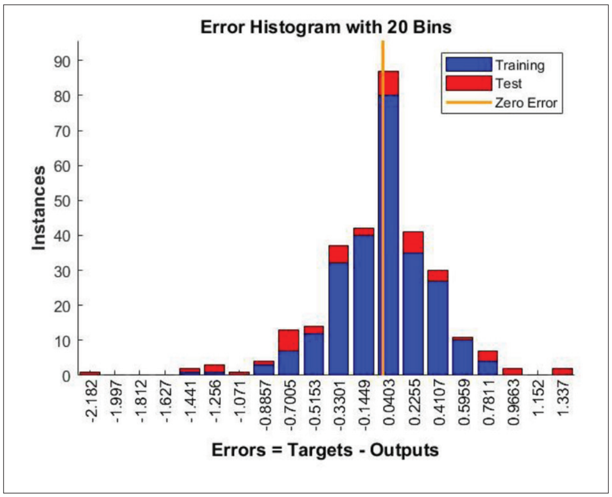

Figure 3. Error plot: the distribution of the difference between the training targets and network outputs for the training and test datasets

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non-linear calibration methods necessary for building robust calibration models since these methods have the potential to model heavy intrinsic non-linearities that can be found in natural multicomponent systems.

Machine learning has also been applied to non-invasive glucose measurements in various ways. This technology provides a way to improve the performance of a glucose monitoring system, and is used in optical, chemical, electrical, and microsensor techniques. The researchers have combined machine learning to investigate glucose levels in patients' blood [23, 24]. Machine learning methods have not only been applied in the tracking of glucose, but also in predicting hypoglycemia [25, 26, 27].

Here, in order to apply the ANN and train it, the MATLAB NFTOOL (The MathWorks, Inc.) program was used.

There are number of batch training algorithms that can be used to train a network, like Levenberg–Marquardt and Scaled Conjugate Gradient. In the network, Bayesian regularization function is used. This function updates the weight and bias values according to the Bayesian optimization method. The network was adjusted in the direction of reducing the error by iteration.

Further improvements in method precision might be expected with additional wavelength ranges, and by instrument improvements that will reduce or cancel noise.

It should be noted that the presented methodology has been shown to detect very subtle glucose variations in non-diabetic patients and that, therefore, this approach is expected to yield even more precise and reliable glucose readings in diabetic HD patients.

CONCLUSION

In this work, a new approach through machine learning and NIR spectroscopy of the spent dialysis fluid has been proposed to improve the fast prediction of blood glucose levels in HD patients. Neural networks have been demonstrated to be remarkably effective in terms of efficiency (training time) and performance ($R > 0.93$). The accuracy and precision of R, for the determination of the concentration of blood glucose obtained using the NIR spectrum of spent dialysis fluid is enough to be useful as a diagnostic screening method. The results confirmed this is a safe, accurate, reliable, and non-invasive method to assess glycemia during HD treatment. The chosen methodology renders its application useful for other pharmacokinetic and pharmacodynamic problems. Further studies on larger patient cohorts would provide valuable results that could be used to design built-in or plate glycemic sensors for dialysis machines. Moreover, machine-learning methods can be used to upgrade the current software in dialysis machines.

Conflict of interest: None declared.

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Праћење концентрације глукозе у крви болесника на хемодијализи коришћењем отпадног дијализата и спектроскопије у подручју спектра блиском инфрацрвеном

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САЖЕТАК

Увод/Циљ Дијабетесна нефропатија води ка трајном оштећењу бубрежног ткива, док сам хемодијализни третман проузрокује осцилације у нивоу глукозе у крви. Неинвазивни мониторинг глукозе, кроз скенирање отпадног дијализата, пружио би значајне информације о нивоу глукозе у крви болесника.

Циљ студије је предикција концентрације глукозе у крви болесника на хемодијализи кроз спектроскопску карактеризацију отпадног дијализата у подручју спектра блиском инфрацрвеном (*NIR*).

Методе Узорци крви и отпадног дијализата узимани су од 15 болесника у 15. минуту хемодијализе. Узорци отпадног дијализата скенирани су у региону *NIR*, који се простирао од 900 до 1300 *nm*. Да би се применила вештачка неуронска мрежа, коришћена је функција *NFTOOL* програмског пакета *Matlab*. Испитивање и обука вештачке неуронске мреже изведени су коришћењем спектра *NIR* отпадне дијализне течности као улаза и концентрације глукозе у дијапазону 3–9 *mmol/l* као излаза.

Резултати Користећи вештачку неуронску мрежу, уочили смо значајну корелацију између спектра отпадног дијализата и концентрације 3–9 *mmol/l* глукозе у крви болесника.

Закључак Корелација од 93% између спектра *NIR* отпадног дијализата и концентрације глукозе показала је да се спектроскопија *NIR* може сматрати неинвазивном методом за поуздано праћење нивоа глукозе у крви код болесника на хемодијализи.

Кључне речи: хемодијализа; машинско учење; отпадни дијализат; спектроскопија *VIS-NIR*; индивидуализовани мониторинг

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