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Employing machine learning to assess the accuracy of near-infrared spectroscopy of spent dialysate fluid in monitoring the blood concentrations of uremic toxins

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Abstract: Hemodialysis (HD) removes nitrogenous waste products from patients' blood through a semipermeable membrane along a concentration gradient. Near-infrared spectroscopy (NIRS) is an underexplored method of monitoring the concentrations of several molecules that reflect the efficacy of the HD process in dialysate samples. In this study, we aimed to evaluate NIRS as a technique for the non-invasive detection of uremic solutes by assessing the correlations between the spectrum of the spent dialysate and the serum levels of urea, creatinine, and uric acid. Blood and dialysate samples were taken from 35 patients on maintenance HD. The absorption spectrum of each dialysate sample was measured three times in the wavelength range of 700-1700 nm, resulting in a dataset with 315 spectra. The artificial neural network (ANN) learning technique was used to assess the correlations between the recorded NIR-absorbance spectra of the spent dialysate and serum levels of selected uremic toxins. Very good correlations between the NIR-absorbance spectra of the spent dialysate fluid with serum urea (R=0.91) and uric acid (R=0.91) and an excellent correlation with serum creatinine (R=0.97) were obtained. These results support the application of NIRS as a non-invasive, safe, accurate, and repetitive technique for online monitoring of uremic toxins to assist clinicians in assessing HD efficiency and individualization of HD treatments.

Keywords: hemodialysis, machine learning, near-infrared spectroscopy, urea, creatinine

Abbreviations: end-stage renal disease (ESRD); hemodialysis (HD); near-infrared (NIR); machine learning (ML); artificial neural network (ANN)

INTRODUCTION

End-stage renal disease (ESRD) is characterized by the progressive retention of uremic toxins, causing clinical manifestations of the uremic syndrome. Even though the definition of uremic toxins also includes inorganic molecules, in clinical practice the term usually refers to organic uremic solutes deriving from protein catabolism. The most assessed uremic toxins in routine clinical practice are urea, creatinine, and uric acid. Hemodialysis (HD) is a life-saving procedure for patients with ESRD. The technique involves the removal of nitrogenous waste products from the patient's blood through a semipermeable membrane along a concentration gradient. Nearly fifty years ago, a dynamic assessment of dialysis performance based

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on urea kinetic modeling was embraced as a parameter of dialysis adequacy to standardize the procedure and provide all patients with the optimum treatment [1]. This estimation relies on a combination of three elements affecting urea concentration: dialyzer clearance (K), dialysis time (t) and body size as represented by urea distribution volume (V), roughly corresponding to total body water [2]. Even though it was introduced at a time when the dialysis population was younger and had fewer comorbidities, membranes were smaller, and the average dialysis time was shorter, the Kt/V_{urea} remains the fundamental estimation of HD adequacy in clinical practice, despite its positive correlation with survival benefit being recently disputed [3-5]. In clinical practice, dialysis adequacy is evaluated monthly, assuming that an equal dialysis dose will be delivered for all remaining treatments. This regular follow-up of HD patients generates an average annual blood loss of 250 to 350mL to routine laboratory testing in already anemic individuals [6]. Post-dialysis urea needed for Kt/V_{urea} calculation requires a 4 mL blood sample and still only provides information related to a single dialysis session which may not correspond to the actual status at any given time [7]. Furthermore, it exposes the medical staff to blood and imposes costs associated with processing and analyzing blood samples.

Alternative methods of urea monitoring have been explored to curtail these downsides. Fully automated online calculation of Kt/V through ionic dialysance of sodium and dialysate UV spectroscopy monitoring have been implemented on some HD monitors to provide the necessary information in real-time without blood sampling or additional costs [8,9]. Both methods offer rapid detection of dialysis inadequacy by continuous monitoring and permit immediate technique adjustments without the need for blood draws. However, there are concerns that ionic dialysance may be associated with interstitial sodium retention due to the spiking of dialysate sodium required for the measurements [10]. In contrast, UV absorbance at any wavelength is not specific for a single substance, and its results are affected by eating during dialysis and fluid infusions [11]. Highly sensitive and selective online urea assays could overcome these potential disadvantages, but this technology is complex and still not commercially available.

Near-infrared (NIR) absorption is another less explored alternative to monitor concentrations of several molecules that reflect the efficacy of the HD process in dialysate samples. The method has been assessed in a modest number of previous scientific works, which mainly focused on determining urea concentration by analyzing the spectra obtained by passing incident NIR light through samples of dialysate fluid and comparing the results with concentrations in standard dialysate solutions with established urea levels or reference dialysate samples [12,13]. Machine learning (ML) is a set of methods related to decision-making mainly based on probability and statistics but more powerful than standard statistical methodologies [14]. This relatively new and highly effective approach automatically detects existing data patterns and uses them to predict future data. The technique has been applied successfully in many fields, including health care [15]. In practice, several ML methods are used. Artificial neural network (ANN) is one type of ML approach modeled to mimic the concept of biological neural networks. It typically has several layers (input layer, one or more hidden layers, and output layer) consisting of interconnected nodes mimicking neurons [14]. Nodes perform the linear transformation of the input data and feed the transformation output to the activation function, which further transmits it to the next layer. Nodes are all assigned a weight, a model parameter that determines the strength of the node's signal. Weights are adjusted through the learning stage with a backpropagation approach to diminish classification errors. ANNs are used for regression and classification problems by dividing the dataset into a training and test set for model training and model validation. Before the training, the number of passes through the entire training dataset (epochs) is determined to optimize learning and assess whether the model is underfitted or overfitted [16].

In the present study, we aimed to evaluate the accuracy of NIR spectroscopy as a method for non-invasive online monitoring of uremic toxins removal by assessing the correlations between the spectra of spent dialysate and coinciding serum levels of urea, creatinine, and uric acid with an ML technique. The aim to provide a non-invasive, real-time assessment of HD treatment efficacy to help modify and individualize this therapy by combining NIR spectroscopy of used dialysate and ML ANN technique has been successfully met in the present study.

MATERIALS AND METHODS

Ethics statement

The research was conducted according to the principles of the Declaration of Helsinki and in compliance with local regulatory requirements. Ethical approval was granted by the Ethics Committee of the Clinical Hospital Center Dr Dragiša Mišović, Belgrade, Serbia (Reference No. 01-1432/14), and all patients gave informed consent for participation.

Subjects and dialysis parameters

Dialysate and blood samples were obtained from 35 ESRD patients on maintenance HD (9 were treated with hemodiafiltration and 26 with high-flux HD) with a standard regimen of three 4-hour dialysis treatments per week. The inclusion criteria were consistent HD prescription in the previous three months, stable intradialytic blood pressure, the absence of physical weakness or dyspnea, and the ability to rest in a 45-90° position during the entire dialysis session. Patients with an active infection, malfunctioning vascular access, and/or intradialytic complications were not included. Patients were continuously monitored during the dialysis treatment according to the standard protocol.

All HD treatments were performed under the usual protocol, with adequate ultrafiltration rates prescribed to remove the interdialytic weight gain. The dialyzer setup and preparation involving a pre-rinse step were performed according to the clinic's standard operating procedure. The dialysis was performed using Dialog+ Adimea® (B. Braun Avitum AG, 34209 Melsungen, Germany) machines. The dialysate solution contained 138 mmol/L Na^+, 110.5 mmol/L Cl^-, 2 mmol/L K^+, 1.75 mmol/L or 1.50 mmol/L Ca^{++}, 1 mmol/L Mg^{++}, 3 mmol/L CH_3COO^-, 32 mmol/L HCO_3^-, 1 g/L glucose. All patients were dialyzed via antebrachial arteriovenous fistulas using a two-needle system and received unfractionated heparin to prevent circuit coagulation. The dialysate flow was set at 500 mL/min, and the mean blood flow rate was 280 mL/min.

Sampling procedures

The samples of the spent dialysate were collected at the midweek dialysis session 15 min after dialysis onset directly from the dialyzer outlet. For each sample, 15 mL of spent dialysate solution was collected in a container and stored at room temperature for approximately 3 h before being transported to the research laboratory. Visible near infrared (VIS-NIR) absorbance spectra of the samples were measured the day after the HD. The blood samples were collected concurrently from the arterial port of the dialysis system, and the concentrations of urea, creatinine, and uric acid were determined on the integrated biochemical analyzer Dimension RxL Max (Siemens Healthcare GmbH, Germany) in the hospital laboratory within 3 h.

NIR spectroscopy

Ultraviolet-visible-near infrared (UV-VIS-NIR) optical absorption spectra of the spent dialysate were obtained using the Lambda 950 (Perkin Elmer, USA) spectrometer equipped with a standard tungsten halogen lamp and a PbS detector. The wavelength region of interest was 700-1700 nm, and the resolution was set to 2 nm. The optical path length was 1 mm. The absorption spectrum of each sample was measured three times, providing a dataset with 315 spectra. The instrument was connected to a Windows 7 operating system PC and was controlled by Perkin Elmer UV WIN LAB Explorer. All measurements were performed in the Laboratory of Nanotechnologies and Nanosystems (Nanolab) at the Faculty of Mechanical Engineering, University of Belgrade, by a single investigator.

Neural network training

NIR absorption values were implemented in the ANN algorithm. In this work, we used a two-layer feedforward network, with a sigmoid transfer function in a single hidden layer and a linear transfer function in the output layer for function fitting. The recorded NIR-absorbance spectra of the spent dialysate were used as input data for the ANN, and targets were corresponding serum levels of urea, creatinine, and uric acid. The ANN was created with an NFTOOL function in the MATLAB® software and trained with the Levenberg-Marquardt algorithm as the fastest method. The Levenberg-Marquardt algorithm is a widely used optimization method for training neural networks. It is particularly effective in scenarios where there are nonlinear relationships between variables and complex optimization tasks. The primary objective of this

algorithm is to minimize the discrepancy between the predicted outputs of the neural network and the desired target outputs [17]. This algorithm has an efficient implementation as a built-in function in the MATLAB® software because the solution of the matrix equation is a built-in function. The algorithm combines aspects of both gradient descent and Gauss-Newton methods. It is known for its efficiency in training neural networks with complex architectures and nonlinear activation functions. MATLAB® provides a highly optimized and reliable implementation of this algorithm, enabling efficient training of neural networks [18]. The training starts with 2 and finishes with 10 hidden neurons. The number of hidden layer neurons is enhanced when the network performance is inadequate. The optimum number of neurons in the single hidden layer in our ANN was determined to be 3. With these settings, the input vectors and target vectors were randomly divided into three sets as follows: 70% were used for training, 15% were used for network validation, and 15% were used as a completely independent test for network generalization. The training data was used to adjust the network weights and biases while minimizing the error value. Network generalization was assessed by using the validation data. The network was adjusted in the direction of maximum error reduction. The training of the network was completed when the generalization stopped improving, as indicated by an increase in the mean square error (MSE) of the validation data samples.

RESULTS

The average serum concentrations of urea, creatinine, and uric acid were 25.01±5.28 mmol/L, 0.97±0.21 mmol/L, and 0.34±0.06 mmol/L, respectively. The following regression plots display the network outputs for training targets, validation, and test set. For a perfect fit, the data should fall along a 45-degree dashed line, representing points where the network outputs are equal to the targets. The circles represent the data points. The correlation coefficient (R) is an indication of the relationship between the outputs and targets. An R value close to 0 indicates a lack of a linear relationship between outputs and targets, while R=1 corresponds to an exact linear relationship between outputs and targets. The correlation was considered excellent if R>0.95 and very good if R was >0.90. The R_{all} represents the value of R for the training data

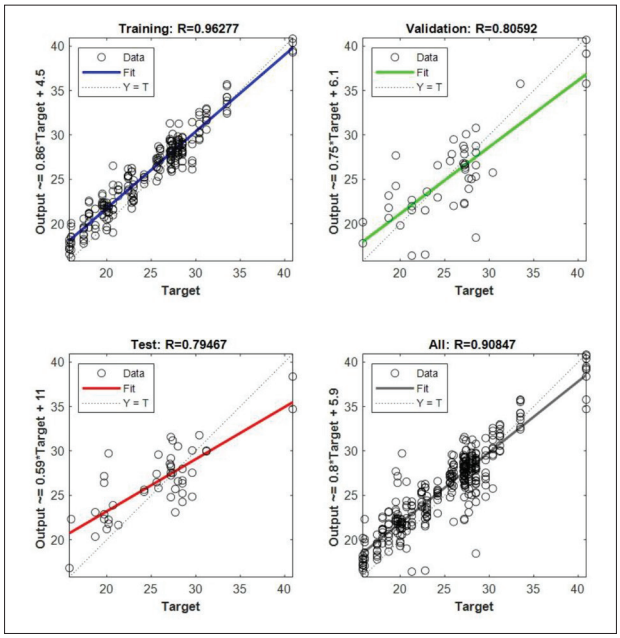

Fig. 1. Regression plot between the NIR absorbance of the spent dialysate and coinciding serum urea concentration in the 15th min of the HD (wavelength 700-1700 nm; the number of spectra used for training was 315). The R_{all} was 0.91. The regression line equation linking the predicted and measured values is Output=0.8Target+5.9.

sets. Regression plots between the NIR absorbance of the spent dialysate and the corresponding serum urea concentrations in the 15th min of HD onset are presented in Fig. 1. The observed wavelength region was 700-1700 nm, and the number of spectra used for training was 315. The following automatically computed equation of the regression line:

$$\text{Output} = 0.8\text{Target} + 5.9$$

provided optimal linking between the predicted (output) and measured (target) values of urea, with a slope of 0.8 and a y-intercept of 5.9. This mathematical representation yielded a Rall value of 0.91, indicating a strong relationship between the predicted and actual values of urea concentration.

Fig. 2 shows regression plots between the NIR absorbance of spent dialysate and the coinciding serum creatinine concentrations in the 15th min from HD session onset within the observed wavelength region of 700-1700nm. The number of spectra used for training was 315. The optimal relation between the predicted (output) and measured (target) values of creatinine was obtained with the following automatically computed equation of the regression line:

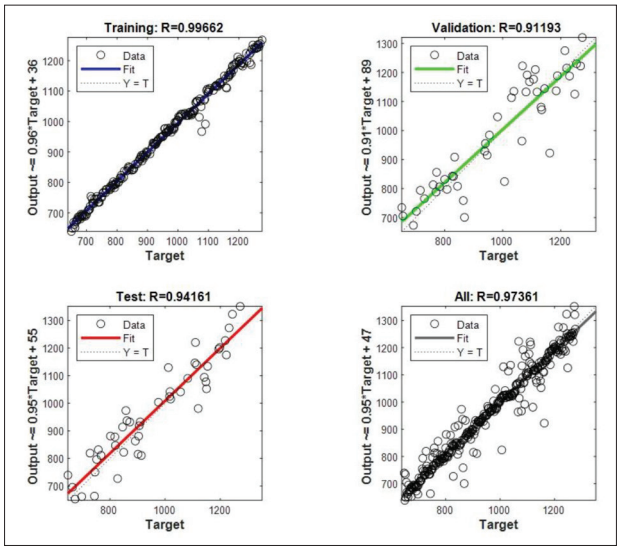

Fig. 2. Regression plot between the NIR absorbance of spent dialysate and the coinciding serum creatinine concentration in the 15th min of the HD session (wavelength 700-1700 nm; the number of spectra used for training was 315). The obtained R_{all} was 0.97. The regression line equation relating the predicted and measured values is Output=0.95Target+47.

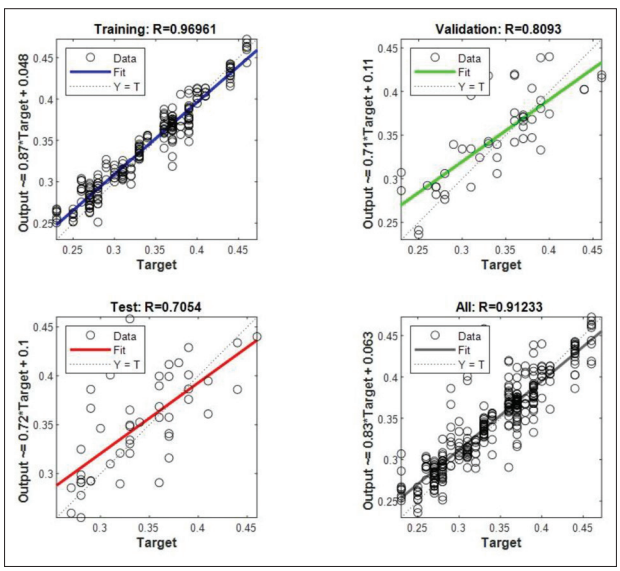

Fig. 3. Regression plot between the NIR absorbance of the spent dialysate and the coinciding serum uric acid concentration in the 15th min of the HD session (wavelength 700-1700nm; the number of spectra used for training was 315). The R_{all} was 0.91. The regression line equation relating the predicted and measured values is Output=0.83Target+0.063.

$$\text{Output} = 0.95\text{Target} + 47,$$

where 0.95 is the slope and 47 the y-intercept. This equation also indicated a significant and positive correlation between the predicted and measured serum creatinine levels with a R_{all} of 97.

Regression plots between the NIR absorbance of the spent dialysate and the coinciding serum uric acid concentrations in the 15th min of the HD session (wavelength 700-1700 nm, number of spectra used for training 315) are presented in Fig. 3. The automatically computed equation of the regression line optimally relating the predicted (output) and measured (target) values of uric acid was:

$$\text{Output} = 0.83\text{Target} + 0.063$$

where 0.83 is the slope, and 0.063 defines the y-intercept. The R_{all} of 0.91 indicates a strong and positive correlation between the predicted and measured serum concentrations of uric acid.

The variations of MSE used for the training, testing, and validation of ANN data for urea, creatinine, and uric acid are presented in Fig. 4. The best validation checks occurred at epochs 7,10, and 15 for urea, creatinine, and uric acid, respectively.

Training, validation, and test parameters were plotted against the best case. The MSE for training and testing sets, quantifying the difference between the network outputs and measured values, were close to 0, implying that the designed ANN was well trained by observing the R and MSE values. The performance plots show that the MSE declines as the number of epochs (one complete sweep of training, testing, and validation) increases. The validation and test set errors have similar characteristics for all parameters, and no significant over-fitting occurred for all cases (where the best validation performance is achieved). These results support the analytical benefit of NIR spectroscopy in detecting selected uremic toxins in the spent dialysate fluid from patients on maintenance HD.

DISCUSSION

The abundance of data generated by the growing number of patients on HD and the large number of dialysis parameters that need to be determined at every treatment

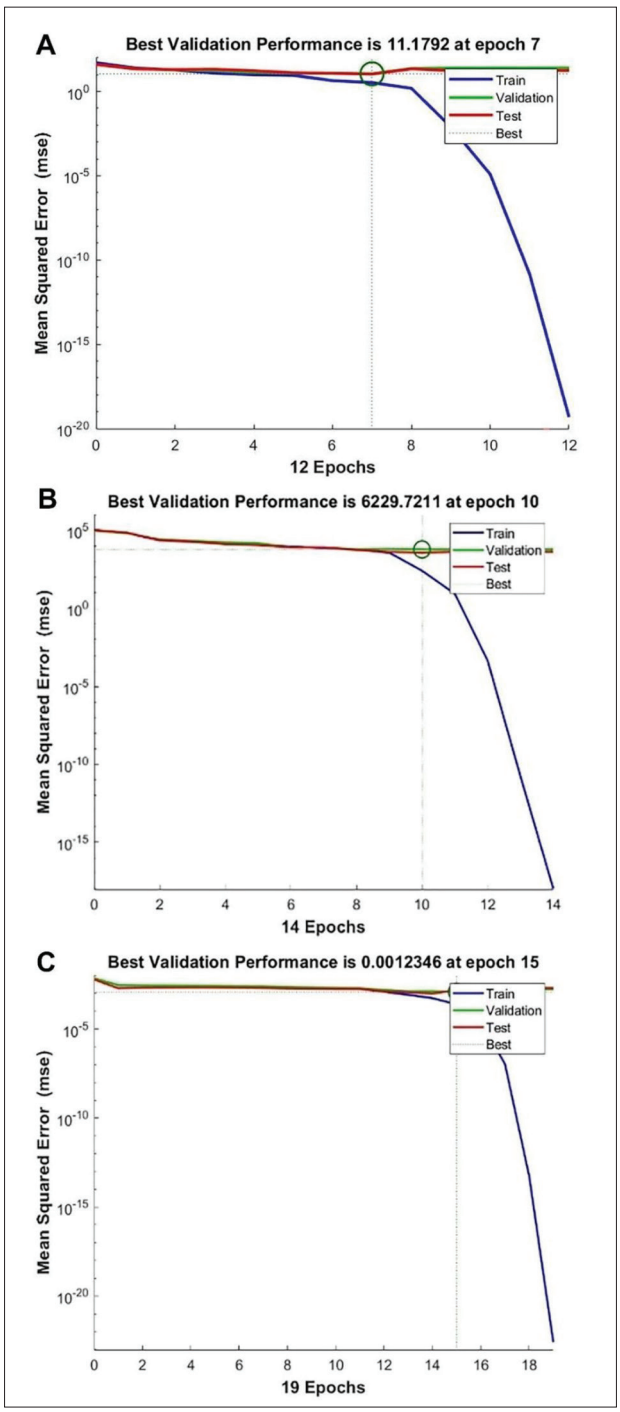

Fig. 4. Variation of MSE for training, testing, and validation data for urea (**A**), creatinine (**B**), and uric acid (**C**) with the number of epochs (iterations). The best validation check occurred at epoch 7 for urea (**A**), at epoch 10 for creatinine (**B**), and at epoch 15 for uric acid (**C**).

session present both an opportunity as well as a necessity to introduce predictive mechanistic models and ML techniques in this area [19,20]. However, ML has only modestly been employed in HD to predict mortality, hematic parameters, hyperglycemia, and dialysis adequacy, and to assist with volume maintenance [19-25]. The NIR data contains a vast amount of information, usually of very high dimensions, allowing the application of ML methods that could be used to improve care in HD patients [26]. For this reason, we hypothesized that NIR spectroscopy could be used as an accurate and non-invasive method for online monitoring of nitrogenous waste compounds in patients' blood based on their removal in the spent dialysate. We performed a NIR spectral analysis of spent dialysate and used an ML algorithm to predict concentrations of these analytes in blood based on the observed NIR spectra, thereby evaluating the accuracy of NIR absorption results. To the best of our knowledge, no previous work has used the ML approach for this purpose.

Quantitative methods for clinical laboratory measurements should be accurate, precise, reliable, rapid, easily automated, and affordable. NIR spectroscopy has the potential to satisfy all these criteria. It requires no reagents and no sample preparation and offers a safe and rapid means of assessing the chemical composition of a wide range of biological samples. The light in the NIR region of the electromagnetic spectrum covering the wavelength range of 750-2500 nm is transmitted through or absorbed by the sample, and the substance concentration is predicted by analysis of the transmitted spectral information. Even information about complex substances can be obtained from a single NIR spectrum. The NIR absorption of biological materials originates from the overtone and combination bands of the molecular vibrations of C-H, S-H, O-H, and N-H bonds, stretching vibrations, and the O-H bending vibrations. These absorption bands are tens of nm wide and relatively weak, with only a small fraction of the absorption of water. When several biologic compounds with comparable concentrations are present in a matrix, the absorption bands may overlap and individually contribute to the observed absorption at any given wavelength. NIR spectroscopy has been applied previously to detect urea in several physiological fluids [27-28], and, more recently, in HD effluent [30]. The NIR spectroscopy appeared to be less suited for creatinine and uric acid in serum due

to the relatively low concentrations of these analytes [31], but in urine, the method rendered sufficiently strong and accurate spectral signature for creatinine [32]. In the present work, we empirically determined the optimal wavelength segment for measuring urea, creatinine, and uric acid to be between 700 to 1700 nm. The region above 1700 nm was excluded as it is strongly dominated by water absorption and temperature.

ML methods offer benefits in recognizing complex correlative relations between the input and output variables when linear regression models are unlikely to obtain valid results [33]. By reducing the utilization of redundant information in input variables during the training process, the ML algorithms produce highly nonlinear decision boundaries, permitting the use of small training data samples and exploiting various forms of medical data that may be latent in nature [34]. ML has been recognized as a helpful tool for decision-making in both diagnosis and medical treatment in different areas of medicine [35]. Nevertheless, it has only recently been applied in the different areas of nephrology to help clinical decision-making [36-40], and so far, to our knowledge, it has not been used to assess the value of NIR spectroscopy of the spent dialysate for monitoring the removal of nitrogenous compounds. When used for this purpose, ML involves the transformation or higher-order combination of spectrum features to perform complex learning tasks and achieve a low training error. In this study, we used the ANN ML method to assess the correlation between inputs and targets. Several batch training algorithms can be used to train a network, including Bayesian regularization and scaled conjugate gradient. In the current study, we opted for the Levenberg-Marquardt backpropagation training function that updates weight and bias values according to the Levenberg-Marquardt optimization method. This algorithm is efficient and adaptive, has stable convergence, and minimizes the nonlinear function [41]. It also appears to be the fastest method for training average-sized feedforward neural networks. It locates the minimum value of the MSE through the iterative process of training, validation, and testing. The proximity of the obtained R values for the training and test sets suggests that the correlation between the network and intended outputs is not coincidental. The MSE values for the training and test sets were close to zero, suggesting that the designed ANN model was well-trained.

The experimental results in this study indicate a very good correlation between the NIR-absorbance spectra of the spent dialysate fluid and serum urea (R=0.91) and uric acid (R=0.91), and an excellent correlation for serum creatinine (R=0.97). The median value of the correlation coefficient for those solutes is high (R_{med}>0.95), and the non-outlier range is very small when calculated over all 35 individual patients for the whole spectrum ranging from 700-1700 nm. Similar conclusions were drawn for online dialysate urea monitoring with NIR, while creatinine performed better in the mid-infrared spectroscopy of artificial dialysate solutions as assessed by partial least square regression [12,13,42].

The high correlations observed in this study may be attributed to the NIR-absorbing properties of the selected solutes as they contribute to the total NIR absorbance. Based on these results, it can be concluded that the accuracy and precision of NIR spectroscopy for urea, creatinine, and uric acid determination is sufficient to perform diagnostic screening compared to standard laboratory measurements. The undisputed advantage of the NIR spectroscopy method is that no specific reagents or preparation are required. Therefore, this method permits repetitive analyses at low cost and without solution pollution to help nephrologists assess the efficiency and modify and individualize HD treatments in real-time. Further improvements in assay precision might be achieved with additional wavelength ranges and by instrument upgrades that would reduce or cancel noise.

Recent decades have brought substantial advances in the care of ESRD patients. Significant efforts have been made to improve dialysis membrane biocompatibility and hemocompatibility, improve the safety of the dialysis procedure, and upgrade the treatment of anemia and secondary hyperparathyroidism [43,44]. Since the number of ESRD patients is increasing faster than the supply of transplantable organs, these developments are of the utmost importance to provide superior treatment and better quality of life for this population. This work adds a potentially valuable tool to these efforts by combining clinical procedures with modern learning technologies. The described technique for monitoring dialysis efficiency by removing small uremic solutes offers grounds for improving the currently available options for tracking dialysis efficacy.

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Author contributions: JTS, VM and BJ conceptualized the methodology and planned the experiments. JTS, IPB, JO and DN organized and implemented all patient-related procedures and bloodwork. VM collected the dialysate samples and performed the spectral analysis, ML computations and data curation. VM and BJ planned and carried out the simulations. VM, BJ, JTS and LM contributed to interpreting the results. JTS and DN wrote the manuscript. DN provided a literature search. JO contributed to project administration. LM supervised the research and supplied the resources. All authors provided critical feedback and contributed to manuscript editing. All authors have read and agreed to the published version of the manuscript.

Conflict of interest disclosure: Authors declare no conflicts of interest.

Data availability: Raw data were generated at the Department of Biomedical Engineering, Faculty of Mechanical Engineering, University of Belgrade. All data underlying the reported findings have been provided as part of the submitted article and are available at: https://www.serbiosoc.org.rs/NewUploads/Uploads/Trbojevic%20et%20al_Raw%20data%20set.pdf

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