Hemodialysis monitoring using mid- and near-infrared spectroscopy with partial least squares regression

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Blood constituents such as urea, glucose, lactate, phosphate and creatinine are of high relevance in monitoring the process of detoxification in ambulant dialysis treatment. In the present work, 2 different vibrational spectroscopic techniques are used to determine those molecules quantitatively in artificial dialysate solutions. The goal of the study is to compare the performance of near-infrared (NIR) and mid-infrared (MIR) spectroscopy in hyphenation with partial least squares regression (PLSR) directly by using the same sample set. The results show that MIR spectroscopy is better suited to analyze the analytes of interest. Multilevel multifactor design is used to cover the relevant concentration variations during dialysis. MIR spectroscopy coupled to a multi reflection attenuated total reflection (ATR) cell enables reliable prediction of all target analytes. In contrast, the NIR spectroscopic method does not give access to all 5 components but only to urea and glucose. For both methods, coefficients of determination greater or equal to 0.86 can be achieved in the test-set validation process for urea and glucose. Lactate, phosphate and creatinine perform well in the MIR with $R^2 \geq 0.95$ using test-set validation.

KEYWORDS
dialysis, glucose, MIR, NIR, PLSR, urea

1 | INTRODUCTION

Hemodialysis is the most common treatment to chronic kidney diseases. At the end of 2013, worldwide 3.2 million people were treated for end-stage renal diseases, whereas 2.5 million were undergoing dialysis treatment (89% hemodialysis and 11% peritoneal dialysis) [1]. In addition, 678 000 persons were living with kidney transplants by this time [1]. Dialysis generally substitutes the detoxification of the human blood using hollow fibers as semipermeable membrane. During the treatment, the patients’ blood is pumped through a filter cartridge consisting of thousands of fibers, whereas the concentration gradient between the blood on the inside and the dialysate on the outside of the fibers results in the transport of small molecules through the membrane. This whole procedure lasts approximately 3 to 5 hours and must be repeated typically every second or third day. In special cases, there are also continuous dialysis treatments in intensive care units, which can last up to 72 hours. The prevalence of end-stage renal diseases varies strongly whereas Taiwan, Japan and the United States show the highest values of 3170, 2620 and 2080 per million people (pmp),
The goal of the present study was to fill this gap and compare the performance of MIR and NIR spectroscopy regarding the determination of urea, glucose, lactate, phosphate and creatinine in dialysate with partial least squares regression (PLSR).

2 | EXPERIMENTAL

2.1 | Samples

Samples were prepared as a 5-component mixture to form an artificial dialysate. To assure uncorrelated variance of the analytes of interest, a “multilevel multifactor design” was applied restricting the number of experiments to the squared number of used concentration levels [12]. This approach enables the coverage of a wide experimental space without excessive preparation of samples. The analytes varying in dialysate in a controlled manner were urea, glucose, lactate, phosphate and creatinine. The concentration ranges of the samples are based on a realistic span of parameter values during dialysis treatments to cover normal as well as extremely pathological cases and can be found in Table 1. In total, \(7^2 = 49\) samples (5 analytes on 7 concentration stages) for calibration and \(5^2 = 25\) for validation (5 components on 5 concentration stages) were prepared. Details regarding this factor design are provided in the Appendix S1 in Tables S2 and S4, Supporting Information.

The samples (exact concentrations provided in Tables S1 and S3) were prepared by mixing a typical dialysate solution (composition given in Table 2) together with the 5 relevant analytes.

2.2 | NIR measurements

For the NIR measurements, a NIRFlex N-500 spectrometer (Buchi AG, Flawil, Switzerland) with the NIRFlex Liquids cuvette add-on was used. The accessible spectral range indicated by the manufacturer was 12,500 to 4000 cm\(^{-1}\) with a wavenumber accuracy of \(\pm 2\) cm\(^{-1}\) and a relative reproducibility of 0.2 cm\(^{-1}\). A total of 32 scans were co-added to result in 1 spectrum. Since temperature is known to be a crucial parameter in NIR spectroscopy, all measurements were taken at 37°C after tempering the samples for 3 minutes since this corresponds to the normal temperature during dialysis treatment. Temperature reproducibility is given with \(\pm 0.5^\circ\text{C}\) (indicated by the manufacturer). Every sample was measured 3 times and averaged afterward. The measurement spot had 2 mm in diameter. The spectra were recorded from 10 000 to 4000 cm\(^{-1}\) in transmission mode. Spectral

![Figure 1](image-url)  
**Figure 1** Global distribution of dialysis patients

| Analyte     | Calibration          | Test-set      |
|-------------|----------------------|---------------|
|             | Conc. in mg/dL | Mean | Median | SD   | Mean | Median | SD   |
| Urea        | 0.00-216.22 | 108.11 | 108.11 | 72.82 | 18.02-198.32 | 113.15 | 117.00 | 66.54 |
| Glucose     | 0.00-324.28 | 162.14 | 162.14 | 109.19 | 27.02-297.26 | 170.20 | 176.00 | 99.77 |
| Lactate     | 0.00-106.88 | 53.44  | 53.44  | 36.00  | 9.01-98.07  | 56.16  | 57.90  | 32.93  |
| Phosphate   | 0.00-28.49  | 14.43  | 14.43  | 9.72   | 2.27-26.12  | 15.12  | 15.60  | 8.86   |
| Creatinine  | 0.00-33.94  | 16.97  | 16.97  | 11.43  | 2.83-31.11  | 17.83  | 18.40  | 10.45  |

Table 1: Concentration ranges of all samples

respectively. The European Union shows an average of 1090 pmp. However, the global average is significantly lower (450 pmp) since the access to proper treatment is still limited. Taking a closer look at dialysis patients in a global content, 45% of the entirety can be attributed to only 3 geographical regions namely United States, European Union and Japan (Figure 1) [1].

Although about 150 to 200 L of dialysate is used for one treatment, there is barely any continuous monitoring except for measuring pH and conductivity. Urea as lead substance for the detoxification process is only determined indirectly or via off-line measurements of discrete samples. Especially for critical patients, a continuous monitoring of different substances can lead to better supervision of the dialysis treatment and can help to avoid critical situations. Spectroscopic methods are known to give access to multiple parameters of interest at a time. They are quick to measure, easy to handle and hardly consume toxic or expensive reagents and are, therefore, often referred to as green science [2]. In clinical settings, spectroscopic methods can avoid expensive reagents and frequent calibration procedures.

In the past, multiple authors reported the successful application of either mid-infrared (MIR) or near-infrared (NIR) enabling online monitoring of urea, glucose, phosphate, lactic acid and creatinine during dialysis [3–10]. However, these processes were not really implemented in clinical settings. In addition, studies using Raman spectroscopy for urea monitoring in dialysate solutions were carried out in the past [11]. Even though this topic was tackled, there is no information comparing the ability of NIR and MIR spectroscopy directly by using the same samples regarding the prediction performance for several relevant analytes. This opens the door for speculations, presumptions and discussions.

The goal of the present study was to fill this gap and compare the performance of MIR and NIR spectroscopy regarding the determination of urea, glucose, lactate, phosphate and creatinine in dialysate with partial least squares regression (PLSR).

### TABLE 1

| Analyte     | Calibration          | Test-set      |
|-------------|----------------------|---------------|
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| Glucose     | 0.00-324.28 | 162.14 | 162.14 | 109.19 | 27.02-297.26 | 170.20 | 176.00 | 99.77 |
| Lactate     | 0.00-106.88 | 53.44  | 53.44  | 36.00  | 9.01-98.07  | 56.16  | 57.90  | 32.93  |
| Phosphate   | 0.00-28.49  | 14.43  | 14.43  | 9.72   | 2.27-26.12  | 15.12  | 15.60  | 8.86   |
| Creatinine  | 0.00-33.94  | 16.97  | 16.97  | 11.43  | 2.83-31.11  | 17.83  | 18.40  | 10.45  |
resolution was set to 8 cm\(^{-1}\) and was automatically interpolated by the software (NIR Ware 1.4.3010) to a data point interval of 4 cm\(^{-1}\). This resulted in 1501 variables per spectrum. A temperature controlled InGaAs detector and HeNe laser with a wavelength of 632.992 nm is built in. An external Teflon reference was measured once a day. The cuvettes used (Hellma GmbH & Co. Kg., Müllheim, Germany) had a technical path length of 2 mm and were made from Quartz SUPRA-SIL 300 providing transmission of >80% in a spectral range of 50 000 to 4000 cm\(^{-1}\) as indicated by the manufacturer. Also 1 mm cuvettes were considered in the beginning of the present study but lower limit of detection (LOD) and limit of quantification (LOQ) values were achieved using 2 mm path length while keeping linearity for the required range.

### 2.3 MIR measurements

MIR spectra were recorded on a FT-MIR spectrometer model ALPHA (Bruker Optics, Ettlingen, Germany) equipped with a pyroelectrical DTGS detector operating at room temperature. The accessible spectral range indicated by the manufacturer was 7500 to 360 cm\(^{-1}\) at a relative reproducibility of 0.04 cm\(^{-1}\). Wavenumber accuracy was given with 0.01 cm\(^{-1}\). As MIR source a globar was used. An attenuated total reflection (ATR) flow through cell with a ZnS crystal providing 4 reflections as described by Roth et al. was used statically [9]. A total of 128 scans with a spectral resolution of 2.04 cm\(^{-1}\) (recorded from 4008-800 cm\(^{-1}\)) were co-added to 1 spectrum. The spectra were automatically interpolated by the software (OPUS 7.2) to a data point interval of 1.02 cm\(^{-1}\). This resulted in 3145 variables per spectrum. Pure dialysate solution (as reported in Table 2) was used as background before each individual sample measurement. All measurements were taken at room temperature, since there is no noteworthy temperature dependence of MIR spectra.

### 2.4 Chemometric analysis

Due to the complex structure and overlapping bands in spectroscopy multivariate approaches (principal component regression (PCR) or PLSR) are often used to establish quantitative models [13]. The most prominent and widely used method is PLSR which uses both the spectral information (X) and the information of the reference values (Y) (Figure 2). The covariance between those 2 matrices is maximized and the original spectra are decomposed into the scores (T), loadings (P) and residuals (E) while Y is decomposed into Q (loading of Y), U (scores of Y) and F (Y residuals) [14].

Linear correlations can be explained by such methods whereas nonlinear relations should be tackled using nonlinear approaches such as artificial neural networks or support vector machines. Whether one faces a linear problem or not can be assessed by analyzing the residuals of the multivariate regression model via the Durbin-Watson test [15]. Calculation of the test value \(d\) is carried out using Eq. (1). Whereas \(r_i\) corresponds to the \(i^{th}\) residual obtained from fitting a straight line to the predicted vs reference plot. If there is no intercorrelation of the residuals described by the Durbin-Watson statistic, then a linear model is appropriate and may be used [16].

\[
d = \frac{\sum_{i=1}^{n-1} (r_{i+1} - r_i)^2}{\sum_{i=1}^{n} r_i^2}.
\]

The usage of the number of latent variables (LVs) for PLSR was tackled via the explained variance by each introduced LV. Overfitting was avoided by not including too many LVs, indicated by reaching a plateau or even a drop in the explained variance plot. Calibration was performed by

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**TABLE 2** Composition of the dialysate solutions

| Ingredient     | Conc. in mg/dL |
|----------------|---------------|
| Na\(^+\)       | 317.26        |
| K\(^+\)        | 15.64         |
| Mg\(^+\)       | 1.22          |
| Cl\(^-\)       | 382.89        |
| HCO\(_3^-\)    | 195.26        |
| CH\(_3\)COO\(^-\) | 17.72        |

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**FIGURE 2** Schematic illustration of PLSR

**FIGURE 3** Raw absorbance NIR spectra of all calibration samples (A). Sections (B) and (C) represent the regression vector intensity in percent referenced to the maximum for glucose and urea, respectively
applying leave-one-out cross-validation [17]. This method enables the efficient usage of available information when only a limited number (n = 49) of samples is present. The best and most preferable way of validation is an independent test-set covering all the expected variation for future applications (concentration ranges, different people taking spectra). Different data pretreatments for NIR spectra were applied, mainly standard normal variate (SNV) [18] and Savitzky-Golay derivatives [19] of different order with varying amount of smoothing points (quadratic polynomial) separately as well as in combination. Also for MIR spectra, various spectral pretreatments were used namely mean centering, first and second Savitzky-Golay derivatives (17 smoothing points) separately as well as in combination. The best performing model was chosen and validated using an independent test-set. However, it is of crucial importance to keep in mind that no pretreatment or multivariate regression method can compensate for poorly designed experiments, bad sampling, bad spectral quality or inaccurately determined reference values [20]. Therefore, particular care was taken for tackling those issues. The NIR data analysis was carried out using the software package The Unscrambler X 10.4 (CAMO Software AS., Oslo, Norway). For the MIR data, the spectral preprocessing and PLSR was performed using the OPUS 7.2 software with the QUANT2 toolbox (Bruker Optics, Ettlingen, Germany). The performance of each constructed PLSR model was

| Model     | PT | Spectral regions in cm$^{-1}$ | Factor | $R^2$ | RMSECV in mg/dL | RMSEP in mg/dL | LOD$_{\text{min}}$ in mg/dL | LOD$_{\text{max}}$ in mg/dL | LOQ$_{\text{min}}$ in mg/dL | LOQ$_{\text{max}}$ in mg/dL |
|-----------|----|-------------------------------|--------|------|----------------|----------------|------------------|------------------|------------------|------------------|
| Urea      | CV | NIR SNV                       | 4      | 0.97 | 12             | —              | 10               | 24               | 29               | 72               |
|           |    | 8648-7348                     |        |      |                |                |                  |                  |                  |                  |
|           |    | 6332-5496                     |        |      |                |                |                  |                  |                  |                  |
|           |    | 4584-4508                     |        |      |                |                |                  |                  |                  |                  |
|           | MIR | mc SG 1/17                   | 4      | 0.99 | 7.9            | —              | 7.3              | 16               | 22               | 47               |
|           |    | 1794-1324                     |        |      |                |                |                  |                  |                  |                  |
|           | TV | NIR SNV                       | 4      | 0.98 | —              | 19             | —                | —                | —                | —                |
|           |    | 8648-7348                     |        |      |                |                |                  |                  |                  |                  |
|           |    | 6332-5496                     |        |      |                |                |                  |                  |                  |                  |
|           |    | 4584-4508                     |        |      |                |                |                  |                  |                  |                  |
|           | MIR | mc SG 1/17                   | 5      | 0.99 | —              | 6.6            | —                | —                | —                | —                |
|           |    | 1794-1324                     |        |      |                |                |                  |                  |                  |                  |
| Glucose   | CV | NIR SNV                       | 4      | 0.89 | 37             | —              | 36               | 73               | 108              | 218              |
|           |    | 9004-8664                     |        |      |                |                |                  |                  |                  |                  |
|           |    | 6320-5756                     |        |      |                |                |                  |                  |                  |                  |
|           | MIR | mc SG 2/17                   | 3      | 0.96 | 22             | —              | 11               | 34               | 33               | 103              |
|           |    | 1451-1324                     |        |      |                |                |                  |                  |                  |                  |
|           |    | 1201-950                      |        |      |                |                |                  |                  |                  |                  |
|           | TV | NIR SNV                       | 4      | 0.86 | —              | 54             | —                | —                | —                | —                |
|           |    | 9004-8664                     |        |      |                |                |                  |                  |                  |                  |
|           |    | 6320-5756                     |        |      |                |                |                  |                  |                  |                  |
|           | MIR | mc SG 2/17                   | 2      | 0.99 | —              | 11             | —                | —                | —                | —                |
|           |    | 1451-1324                     |        |      |                |                |                  |                  |                  |                  |
| Lactate   | CV | NIR —                        | —      | —    | —              | —              | —                | —                | —                | —                |
|           |    | 1777-1700                     |        |      |                |                |                  |                  |                  |                  |
|           | MIR | mc SG 1/17                   | 5      | 0.95 | 8.3            | —              | 6.5              | 14               | 20               | 43               |
|           |    | 1777-1700                     |        |      |                |                |                  |                  |                  |                  |
|           |    | 1201-1075                     |        |      |                |                |                  |                  |                  |                  |
| Phosphate | CV | NIR —                        | —      | —    | —              | —              | —                | —                | —                | —                |
|           |    | 1201-950                      |        |      |                |                |                  |                  |                  |                  |
|           | MIR | mc SG 1/17                   | 8      | 0.99 | 3.0            | —              | —                | —                | —                | —                |
|           |    | 1201-1075                     |        |      |                |                |                  |                  |                  |                  |
| Creatinine| CV | NIR —                        | —      | —    | —              | —              | —                | —                | —                | —                |
|           |    | 1777-1700                     |        |      |                |                |                  |                  |                  |                  |
|           | MIR | mc SG 1/17                   | 5      | 0.98 | 1.5            | —              | 1.9              | 3.5              | 5.8              | 11               |
|           |    | 1201-1075                     |        |      |                |                |                  |                  |                  |                  |
|           | TV | NIR —                        | —      | —    | —              | —              | —                | —                | —                | —                |
|           |    | 1777-1700                     |        |      |                |                |                  |                  |                  |                  |
|           | MIR | mc SG 1/17                   | 4      | 0.96 | 2.1            | —              | —                | —                | —                | —                |
|           |    | 1576-1075                     |        |      |                |                |                  |                  |                  |                  |

Abbreviations: -, value not available; PT, data pretreatments; mc, mean centering; SG x/y, Savitzky-Golay derivative (x, derivative order; y, number of smoothing points); SNV, standard normal variate; CV, cross-validation; TV, test-set validation.
additionally assessed by calculating the multivariate LOD and LOQ (LOD$_{\text{min/max}}$/LOQ$_{\text{min/max}}$) intervals referred to the IUPAC-Consistent Approach postulated by Allegrini and Olivier [21, 22]. For compact illustration of all regression vectors (resulting from the PLSR), they are displayed as heatmaps which is a color-coded representation of the vectors. The maximum value (positive or negative) from 0 is set to 100% and all other values are put into relation. Blue corresponds to strongly negative signals whereas red indicates strong positive amplitudes.

3 | RESULTS AND DISCUSSION

3.1 | NIR results

All raw NIR spectra used during calibration are shown in Figure 3A. Applying PLSR (including mean centering) to this data set results in regression models described by the number of factors (= LVs), the coefficient of determination ($R^2$), the root mean square error of cross validation (RMSECV) / root mean square error of prediction (RMSEP) and corresponding LOD$_{\text{min/max}}$/LOQ$_{\text{min/max}}$ (Table 3). Analyzing the Durbin-Watson statistics (at 5% significance level) showed that nonlinearity is not significantly present due to the $d$-value (calculated via Eq. (1)). The regression vectors of the corresponding PLSR results are represented as heatmap in Figure 3 in section (B) for glucose and for urea (C) in percent referred to the maximum value. In addition, they are presented as raw regression coefficients in the Figure S1. As spectral pretreatment, SNV was used for the selected spectral range. By taking a closer look at Table 3, one can see that using NIR spectra led to regression models for urea and glucose with a $R^2 \geq 0.86$. Applying independent test-set validation showed that using this model gives access to the glucose and urea amount. The spectral ranges used were 8648 to 7348 cm$^{-1}$, 6332 to 5496 cm$^{-1}$ and 4584 to 4508 cm$^{-1}$ for urea and 9004 to 8664 cm$^{-1}$ and 6320 to 5756 cm$^{-1}$ for glucose. Since no characteristic vibrations are observed in the experimental data, the main explanation is the distortion of molecular water patterns reflecting the analyte concentration indirectly. However, for the analytes lactate, phosphate and creatinine no satisfactory models could be established. This fact is mainly attributed to the generally lower concentrations of those 3 analytes (see Table 1) and to the lack of sufficiently intense signals in the NIR region of phosphate. Considering the LOD and LOQ values of the constructed regression models, one can observe that these values are high compared to the mean values of the measured ranges. This is mainly attributed to the diverse sample composition. The RMSEP represents the average deviation over the whole regression model which is the reason why it does not optimally reflect scattering of the prediction. Therefore, combining the LOD/LOQ and RMSEP values gives a deeper insight into the actual performance and limitations of the models.

3.2 | MIR results

Figure 4 illustrates all raw MIR spectra from the calibration sample set as difference to the background dialysate solution (composition as in Table 2) resulting in relative absorbance values (positive and negative). Due to the vibrations in the MIR range, (fundamental vibrations) interpretative signals can be observed for the analytes. Hence, regression models for all analytes could be established. Durbin-Watson test (at 5% significance level) justified the application of linear models. The results for each analyte are given in Table 3. Promising coefficients of determination for all components were achieved with a $R^2 \geq 0.95$. In contrast to the NIR results, lactate, phosphate and creatinine were predicted with high accuracy. Spectral pretreatments were mean centering for all models followed by Savitzky-Golay first derivative using 17 smoothing points for urea (1794-1324 cm$^{-1}$, 1201-1075 cm$^{-1}$), lactate (1777-1699 cm$^{-1}$, 1576-1324 cm$^{-1}$, 1201-1075 cm$^{-1}$) and creatinine (1777-1700 cm$^{-1}$, 1576-1075 cm$^{-1}$). Savitzky-Golay second derivative using 17 smoothing points was applied for glucose (1451-1324 cm$^{-1}$, 1201-950 cm$^{-1}$). For phosphate (1201-950 cm$^{-1}$), no pretreatments except mean centering were necessary. The used spectral ranges for each individual component are indicated in brackets. Regression coefficients are illustrated for all analytes as heatmap in Figure 4 (additionally, classical regression coefficients plots are provided in Figure S2). Taking a closer look at the RMSECV and RMSEP results, one can conclude that...
MIR performs better than NIR-in all cases. Moreover, the LOD_{min/max} interval is in the same order of magnitude as the RMSECV.

4 | CONCLUSION

The observable signals in the MIR range appear to be more suited for the present application than the ones in the NIR range. The strong absorptivity of water (see Figure 3) overlays the specific signals occurring from the analytes of interest. Even the use of chemometric tools cannot compensate for this lack of selectivity in NIR spectroscopy. Looking at the results of this study, it can be concluded that MIR should be preferred for monitoring hemodialysis because it gives access to more analytes of interest. However, even those components that can be monitored using NIR are predicted with greater accuracy when MIR measurements are taken. Despite the fact that NIR spectroscopy is for many applications superior to other vibrational methods because of easier operation and greater layer thickness none of these advantages can compensate for the lack of intense signal of the spectral range. An additional problem is the interference with the aqueous matrix resulting in saturation of a broad spectral range. Taking these results into consideration, the aim of the study, which was to directly compare the ability of MIR and NIR spectroscopy was fulfilled. Therefore, further studies should focus on the implementation of MIR spectrometers for the quantification of dialysate relevant small molecules.

CONFLICT OF INTEREST
The authors declare no conflict of interest.

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Please see Supporting Information online.

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SUPPORTING INFORMATION
Additional Supporting Information may be found online in the supporting information tab for this article.

Appendix S1. Supporting Information
Table S1 calibration samples, 5-component mixture in dialysate, concentrations
Table S2. calibration samples, 5-component mixture in dialysate, level design
Table S3. validation samples: 5-component mixture in dialysate, concentrations
Table S4. validation samples: 5-component mixture in dialysate, level design
Figure S1. Regression coefficients (B) from PLSR with NIR spectra for urea (A) and glucose (B)
Figure S2. Regression coefficients (B) from PLSR with MIR spectra for urea (A), glucose (B), lactate (C), phosphate (D) and creatinine (E)

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