Multi-sensor data fusion for non-invasive continuous glucose monitoring

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Abstract – Measurements of impedance spectra used for non-invasive glucose monitoring are affected by a variety of perturbing factors such as temperature and sweat/moisture fluctuations, changes in perfusion, and body movements. In order to quantify and compensate for these perturbing effects, a multi-sensor approach was suggested. Different sensors are used, measuring signals correlated with blood glucose and perturbing factors, respectively. Here, we investigate how the multiple sensor data can be transformed into meaningful information about changes in the concentration of blood glucose. Linear regression models and variable selection (stepwise forward/backward and lasso) techniques are used to derive generally valid models allowing for the estimation of blood glucose concentration. We find that over-fitting is best avoided by using a special version of cross-validated prediction error as the model selection criterion. Indeed, the resulting models are reasonably small, plausible, and comprise an additive adjustment for the experimental run.

Keywords: Statistical modeling, multiple sensors, glucose monitoring.

1 Introduction

Over a certain frequency range, impedance (complex resistance) of the skin is correlated with changes in glucose concentration. Using capacitive fringing field sensors, impedance spectroscopy (IS) allows for measuring skin (and underlying tissue) impedances non-invasively and continuously over a wide frequency range. Therefore, in principle, IS can be used for non-invasive continuous glucose monitoring [1]. However, above all in daily-life situations, the skin impedance spectra are not only correlated with glucose changes, but also affected by a variety of other factors that perturb the determination of glucose concentration. Relevant perturbing factors are, e.g. temperature fluctuations, variations of the skin moisture and sweat, changes in perfusion characteristics, as well as body movements affecting the sensor-skin contact [2] [3]. A glucose monitoring technology based on impedance spectroscopy must therefore also possess the capability of quantifying and compensating for the different perturbing effects. To address these aims, a multi-sensor platform was developed. Each sensor of this platform is non-invasive and continuously records a signal that is either correlated with glucose (primary signals, sampling rate = 0.02 Hz) or one of the perturbing factors (secondary signals, sampling rate ≤ 0.02 Hz) that are considered to be relevant. Effects of changes in the blood glucose concentration on the impedance spectrum, for instance, are discussed in [4] [1]. The ability of the secondary sensors to track the perturbing effects is investigated in [5].

In order to test the multi-sensor concept, i.e., to verify if the primary and secondary signals recorded by the multiple sensors can be transformed into meaningful information about the concentration of blood glucose, an experimental clinical study was carried out, in which the blood glucose concentration of healthy subjects and patients with diabetes type I/II was varied under controlled conditions with subjects lying in bed. One of the study goals was to derive a suitable statistical model with an adequate predictive power (i.e., exempt from over-fitting). In order to achieve this, different regression techniques as well as shrinking and variable selection methods are investigated.

2 Methods

2.1 Subjects and Protocol

The multi-sensor concept and data fusion process is investigated in patients with diabetes and healthy subjects. The data was acquired in a clinical experimental study in which 4 patients with diabetes mellitus type I (age: 35.8 ± 10.4 years, BMI: 23.8 ± 1.6 kg/m², HbA1c: 7.0 ± 1.7%), 3 patients with diabetes mellitus type II (age: 57.0 ± 11.4 years, BMI: 24.7 ± 3.8 kg/m², HbA1c: 6.7 ± 0.7%) and 4 healthy subjects (24.5 ± 4.5 years, BMI: 21.4 ± 1.6 kg/m²) participated.

Using an intravenous glucose clamp technique [6], the blood glucose concentration of a subject was varied during a ten hour study day according to a predetermined profile including two hyperglycemic events (Figure 1).

Figure 1: Glucose profile determining the variation of the blood glucose concentration of a subject during a study day.

The blood glucose concentration was the only variable that was tightly controlled. The fluctuations of the other relevant variables were either a response to the change of the glucose concentration or due to glucose independent physiological and environmental variations such as changes of the environmental temperature, which during a run typically fluctuated in a range of ± 1.5 °C. Here, a run
refers to a glucose clamp trial carried out on a single subject during a study day.

All except one subject completed two runs. Therefore, a priori there are 21 study-runs available for the derivation of a predictive statistical model. However, a first inspection of the data shows that 3 runs are incomplete or include unusable measurements, so that not all runs can be considered in the modeling process. Most sensor signals of the very first run are extremely noisy and the primary signals do not show a visible correlation with the glucose variation. The reason for this was the presence of a large quantity of sweat and moisture at the sensor-skin interface due to an unsuitable taping style of attachment of the sensor housings on the skin and the poor temperature and humidity control that we initially achieved in the study room. Therefore, the first run is not considered for the modeling process. In order to prevent an excessive accumulation of sweat/moisture at the interface, the attachment of the sensor housing was changed afterwards to allow for aeration and additional air-conditioning capacity was installed in the study room. Moreover, 2 runs are discarded due to multiple contact problems of the impedance sensor with the small penetration depth of the electromagnetic fields (see Sect. 2.2 for details). In summary, 18 of the 21 runs are used for the statistical modeling.

2.2 Sensors and Data

Here the different sensors, their purpose as well as the preprocessing of the sensor data are discussed.

A capacitive fringing field sensor is used to determine the impedance of the skin and underlying tissue by measuring the response to an externally applied alternating electric field with frequencies in the range of 1 – 200 MHz. The sensor features the ability to achieve different penetration depths of the electromagnetic field (EMF) into the various tissue layers by utilizing two sets of electrodes with electrode separations of 0.2 mm and 4 mm. For convenience, the electrodes associated with the deeper (4 mm) and less deep (0.2 mm) penetration of the EMF are referred to as long and short sensor respectively. The signal of the long sensor is our primary signal. Its EMF penetrates not only the upper skin layers but also the lower ones that are mainly affected by glucose changes. Thus, glucose variations are mainly seen in the “long” signal. The short sensor penetrates only the upper skin layers. Its signal is therefore much less sensitive to glucose variations, but it contains information about perturbing effects due to non-glucose related variations of the dielectric properties of the upper layers, that also contribute to the long signal. In principle, it can therefore be used to compensate the long signal for the perturbing effects of the upper skin layers.

An optical sensor is used to measure the optical properties of the skin and underlying tissue over a wavelength spectrum ranging from the infrared to the visible. The sensor consists of two commercially available microspectrophotometers (Microparts GmbH) and a custom designed optical sensor head comprising a fiber-optic transmitter and two receivers measuring at two separation distances from the input light source. It is assumed that the signals (reflection intensity) from the different spectral ranges are correlated with different perturbing factors. Indeed, investigations with optical spectrometers suggest, that the diffuse reflection in the skin and underlying tissue at a wavelength of ~ 500 nm (green light) is associated with the perfusion, i.e., micro-vascular blood circulation. Furthermore, the results suggest a relation between reflection at ~ 600 nm (red light) and the amount of oxygen in the blood as well as a connection between reflection at ~ 800 nm (infrared light) and water.

Skin and underlying tissue hydration levels, that also affect the primary signal, are monitored with a sweat/humidity sensor comprising an interdigitated electrode utilizing a galvanic response based measuring technique.

The pressure applied to the sensor as well as its acceleration and position relative to the center of gravity are continuously monitored using an integrated piezoelectric sensor and accelerometer, respectively.

Furthermore, the skin surface temperature and ambient humidity close to the impedance sensor is monitored using a commercially available data logger.

These sensors are attached to skin according to the schematic illustration in Figure 2.

To assure close monitoring of the glucose concentration, changes in the blood glucose concentrations are measured from intravenous blood samples every 5 min with a HemoCue Glucose 201 Analyzer (HemoCue AB, Sweden).
at the bedside during glucose changes and wherever necessary for medical purposes.

As stated above, several spectra were measured with our multi-sensor platform. Counting, the signal at each sampled frequency individually, the multiple sensors record thousands of signals that potentially are either correlated with the glucose or some perturbing factor. However, there is a lot of redundancy in the spectra. Therefore, the dimension of each spectra is in a first approach reduced by averaging over a low, middle and high frequency band. That is, the relevant information of the impedance spectra is supposed to be given by three spectral mean values. The selection of the boundaries of the frequency bands was based on a visual inspection of the spectra. Regarding the optical spectra, it is a priori assumed that the two wavelength peaks as well as the local minimum in between contains additional relevant information. Therefore, in addition to the three means, the intensities at these local extrema are used as input variables. In fact, the averages of the frequency bands is not calculated for the spectral values but for the log-transformed spectral values. This is discussed in greater detail in the next Section.

3 Regression Techniques

3.1 Linear models

A general model connecting the response or target variable \( Y \) to a number of explanatory variables \( x^{(1)}, \ldots, x^{(m)} \) is a regression model of the form:

\[
Y_i = h(x_i^{(1)}, \ldots, x_i^{(m)}) + E_i
\]

(1)

where \( h \) is the regression function and \( E_i \) denotes the deviations of the response value \( Y_i \) for the \( i \)th observation from the value of this function, evaluated for the respective values of the explanatory variables \( x_i^{(1)}, \ldots, x_i^{(m)} \). The common assumptions about the deviations \( E_i \) are:

- \( E_i \) follows a normal distribution,
- the variance of \( E_i \) does not depend on \( i \), and
- the deviations are stochastically independent.

In brief, this is denoted by:

\( E_i \sim N(0, \sigma^2) \), independent.

In the present application, the response variable is blood glucose concentration as measured by the intravenous glucose clamp in the experiment, or any transformation of it, and the potential explanatory variables are all sensor measurements. Counting all sampled frequencies of all spectra individually there are 3000 such variables. After, the dimension reduction there still remain 35 input variables.

The simplest useful form of a regression function is a linear function, written as \( \beta_0 + \beta_1 x_i^{(1)} + \ldots + \beta_m x_i^{(m)} \).

Since the observations are best characterized by a run number \( r \) and a time index \( t \), the basic model can be written as

\[
Y_{rt} = \beta_0 + \beta_1 x_{rt}^{(1)} + \ldots + \beta_m x_{rt}^{(m)} + E_{rt}
\]

(2)

The model implies additive linear effects of the variables \( x^{(i)} \). It is important to note that rather complicated relationships can be brought into this form:

- The variables obtained from actual measurements – from sensors in our application – can be transformed. In fact, log transformations are applied to all spectral signals (prior to the dimension reduction), the acceleration, the pressure and the sweat/moisture measurement. The response is transformed in a more complicated way.
- Non-additive effects can be incorporated by adding interaction terms to the model formula, often in form of a product of two variables as a term \( \beta_k x_i^{(n)} x_j^{(m)} \). Adding all possible interactions between all variables leads, for 35 variables, to 35 \( 34/2 = 1190 \) terms, however, and is therefore recommendable only for small numbers of variables.

The coefficients \( \beta_i \) characterizing the regression model need to be estimated from the experimental dataset in which the response variable has been measured. If the assumptions about \( E_i \) mentioned above were fulfilled, then the method of Least Squares would be optimal for this estimation. In practice, the method is used even though the assumptions are not plausible in our application (and in many others). This issue is described in more detail in Section 5.

3.2 Model selection

A regression model with 35 explanatory variables is not useful in practice because:

- one goal of the analysis often is to find out which variables really do have an influence on the response variable, and more importantly here,
- if the goal is to provide accurate predictions of \( Y \) on the basis of the \( x^{(i)} \)’s in the future, such predictions get worse by including too many variables in the model.

Useful models therefore only include a subset of the potential explanatory variables, and it is an important step in the analysis to select this subset on the basis of the experimental data set.

The most important ingredient of a model selection procedure is a criterion that measures the merit of any model that might be considered. If the goal is prediction, the criterion should quantify the variability of prediction errors. The most well-known criterion is Akaike’s Information Criterion (AIC) [7].

\[
\text{AIC} = n \log(\text{SSE}/n) + 2p
\]

(3)

where SSE is the sum of squares of the residuals, \( n \) is the number of observations, and \( p \), the number of coefficients. It joins a first term measuring the variability of the
residuals, and a second term which increases with the number of coefficients $\beta_j$, used in the model, often called the penalty term. The weight of this term depends on the number of observations $n$ and is derived under the assumption of independent $E_i$.

The term is needed because the residuals are calculated from the fitted values obtained for the same observations that were used to estimate the coefficients. Their scatter therefore underestimates the variability of the. $E_i$ and the term aims to correct this bias.

Alternatively, the dataset can be split into two parts, one being used to estimate coefficients and the other, to obtain prediction errors with the correct variability.

**Cross validation** does this by using all but one observation for estimation and obtaining a single “unbiased” prediction error – but doing this in turn for all observations [7]. The variance of these $n$ prediction errors then yields a suitable criterion for model quality. It is equal to the mean square of the so called Studentized residuals. The same idea is often applied leaving out more than one observation at a time. **$k$-fold cross validation** first splits the observations randomly into $k$ blocks of (almost) equal size and then estimates coefficients from all observations except one block, using the block to evaluate the predictive errors. We will apply this technique in a modified form in Section 4.2.

Given a criterion for the quality of models, the problem is to find the model that optimizes it. The number of models of the form (2) is $2^m$. An exhaustive search done by simply calculating the criterion for all models, called “all subsets regression” is therefore feasible for $m$ smaller than 15 or 30, depending on the speed of computing. A cheap alternative is the traditional **stepwise backward elimination method**. Starting from the “full model” including all $m$ variables, the one variable leading to the largest gain in quality is removed in each step until the criterion starts to turn worse by dropping the next variable. The reverse is also in use: The **stepwise forward selection method** starts by picking the variable most correlated with the response and then adding one variable in each step until the criterion deteriorates. Both methods are instances of a “greedy algorithm” for finding the optimum. They may miss the true “global” optimum and can lead to different results. Here, we use the backward method.

### 3.3 Collinearity

The explanatory variables are often highly correlated. While this does not violate any assumption of the model, it leads to several difficulties with interpretations of results:

- Coefficients of such variables show a high standard error, since their effects can “substitute each other”. This phenomenon is called variance inflation.
- If a future observation should not follow the close relationship, its predicted value would be ill-determined.

The second point is relevant for our application. It can be alleviated by using alternative methods for estimating the coefficients as discussed in the next subsection.

The problem is not restricted to pairs of variables that are highly correlated but also arises for larger sets of variables that show approximately a linear relationship among them. Such sets are called, as in Linear Algebra, “collinear variables”.

### 3.4 Shrinkage and the Lasso method

A basic idea to reduce the problem of exceedingly variable predicted values is to avoid “big” estimated coefficients by punishing them. This is achieved by adding a respective term to the criterion optimized in the estimation step – usually the sum of squares of residuals, thus using:

$$\text{SSE} + \lambda \sum |\beta|$$

Here, $\lambda$ is the penalty factor which can be chosen to obtain a suitable weight of the penalty. If $q=2$, the Euclidean norm is used to measure the size of the coefficient vector, and the method is called **ridge regression**. More recently, the method with $q=1$ has been proposed under the name of **Lasso method** [8]. Since it leads to a quadratic programming problem, it is not surprising that its solutions often include coefficients $\beta$ that are exactly zero. Such coefficients are akin to dropping the respective variables from the model. Thus, the Lasso method can be used as a technique for model selection.

The size of the penalty factor $\lambda$ will determine the size of the model selected in this way. The criterion proposed along with the method to choose this factor is cross validation as discussed above.

The coefficients will be changed by rescaling the $x$ variables of the model, thereby changing the relative weight they get in the penalty term. Therefore, the $x$ variables are standardized to variance one. Moreover, it is intuitively clear that a data-depending scaling – equivalent to using a weighted sum $\sum w_j |\beta|$, as the penalty term – may improve the results of the procedure. Thus, the “adaptive lasso” proceeds in two stages [9]: After obtaining first lasso estimates $\beta_j^0$ based on cross validation, the penalty term in (4) is replaced by the penalty term with weights $w_j = 1/|\beta_j^0|$. This leads to relatively large penalty of coefficients that turned out to be small in the first stage.

A strong point of the lasso method is an efficient algorithm called LARS to calculate the solutions simultaneously for all values of the penalty parameter $\lambda$ [10].
In our application, the factor variable run plays a special role. It is needed for obtaining acceptable results. However, current implementation of the lasso method (in the statistical software R) cannot handle factors adequately. Therefore, we centered all variables within runs about the run means and applied the algorithm to the centred data. This procedure yields the required results.

4 Results

4.1 Traditional selection criteria

A model was first derived for each run separately using backward and forward stepwise methods with AIC. This yielded excellent fits, i.e., the glucose profile can be very well fitted by models based on the sensor data. However, the models strongly vary from run to run. Since these models differ not only from person to person, but also between different runs of the same person, they do not reflect a general relationship. Therefore, the models resulting from the regression analysis of individual runs can not be used for a prospective application. Therefore, the complete data set combining the data from all runs is used to derive general (universal) models. All subsequent analyses were carried out on this “pooled” data set. The nominal variable “run” is added to the data set. The consequences of its use in regression models is addressed in Section 5.

An initial modeling round focused on the analysis of data from healthy subjects and patients with type 1 diabetes (T1DM). The pooled data set used for the analysis combined the data of 13 runs from 4 healthy subjects (age: 24.5 ± 4.5 years, BMI: 21.4 ± 1.6 kg/m²) and 4 T1DM patients (age: 31.0 ± 5.3 years, BMI: 23.5 ± 1.8 kg/m², HbA1c: 6.5 ± 1.7%). A first set of tentative models was obtained by applying backward and forward stepwise methods with standard model selection and validation criteria (AIC, R²). A model with 9 variables and a predictive power that is tentatively deemed suitable was presented in [11]. The plot, comparing the predictions of the model together with actual values of the target variable (i.e., the invasively measured blood glucose levels) is reproduced in Figure 3.

Here, we present the results of the empirical data modeling process using besides data of healthy and T1DM subjects also data of patients with diabetes mellitus type 2 (T2DM). All subsets regression using the AIC criterion was applied to the pooled data set combining the data of 18 runs from 4 healthy subjects, 4 T1DM and 3 T2DM subjects. Stepwise forward selection was used to check if the resulting model should be complemented with some

![Figure 3: Comparison of model prediction with reference glucose. Black line: Time series of reference glucose. Dashed line: Fitted values, i.e. model predictions (the “pooled” data set of the normal and Type 1 subjects, i.e., all 13 runs are used to derive the model; which then is applied to the explanatory variables of each run).](image)
interaction terms. Furthermore, residual analysis suggested a specific transformation of the response variable. The resulting model consists of 9 continuous explanatory variables, and an additive constant. Besides variables representing long and short impedance signals, the models include a temperature variable and an acceleration variable. As no interaction term involving the run factor was included, the effects of all the explanatory variables on the response is modeled to be the same for all runs.

However, the model contains the run factor itself, which allows for an additive constant specific to each run.

Figure 4 shows the fitted values according to this model together with the actual values of the target variable as functions of time for all runs. An adequate agreement is generally attained, but there are some episodes with larger discrepancies.

The predictions for run 151 are significantly worse than those of the other runs, suggesting the occurrence of some measurements problems. Dropping this run from the analysis leads to much more plausible results. Examining the nature of the explanatory variables that appear in the model, some doubts arose whether the model was adjusted too closely to the actual data set, and a more restricted model would supposedly give better results for future runs.

4.2 Cross validation on runs

In fact, the criterion AIC used to choose the size of the model relies on independent random deviation $E_{\text{res}}$ and so do the cross validation methods discussed in Section 3.3. It is obvious that subsequent residuals within the same run are highly correlated.

Figure 4 : Comparison of model prediction with reference glucose. Black line: Time series of reference glucose. Dashed line: Fitted values, i.e. model predictions (the “pooled” data set, i.e., all 18 runs are used to derive the model; which then is applied to the explanatory variables of each run). Dotted line: “Cross validated” fitted values (all but one run is used to derive the model; the model is then used to estimate the glucose of the omitted run; the procedure is repeated 18 times).
On the other hand, the $E_{ir}$ from different runs $r$ can plausibly be assumed to be independent. Therefore, the idea of a k-fold cross validation is adapted to this situation by using the runs as blocks: Estimation of coefficients is done using all runs but one, and predicted values are calculated for all observations of the run that was left out.

The mean squared prediction error was then calculated. This is done for all runs in turn, and the averaged prediction errors were used as the quality criterion for the model.

The procedure also yields the set of “cross validated” fitted values. They are shown in Figure 4 along with the ordinary ones. Clearly, the two kinds of fitted values are very different for run 151. This means that the model for the whole data set was adjusted considerably to fit the peculiarities of run 151.

Since, the goal is to provide accurate predictions of the target variable on the basis of the explanatory variables in the future, i.e., to derive generally valid relationships, this is an undesired effect, that might lead to over-fitting and consequently considerably affects the model selection process.

In order to take the existent temporal dependencies correctly into account in the model selection procedure, the criterion introduced above (i.e., the cross validated mean squared prediction error using runs as blocks, hereafter referred to as cv) is used in conjunction with stepwise procedures as well as the lasso method. The resulting models are smaller and attain predictive power that is only slightly worse. The models do not include an optical signal and consist of 4 and 5 variables in addition to the run factor, respectively. Considering the size of the models and the nature of the explanatory variables, we are this time more confident that no dominant over-fitting is present and that the models are able to reproduce at least some relevant aspects of the dynamics of the glucose variations based on future explanatory variables.

Figure 3 shows the criterion cv as a function the shrinkage factor $s$, which is a reparameterization of the lasso penalty parameter $\lambda$ and indicates how the number of variables decreases. The lasso method suggests that the model with the best predictive power is the one that has the smallest cv, which is here a model with about 5 variables.

5 Discussion and conclusions

These are the first data analyses activities with sensor signals from the multisensor concept suggested and under development at Solianis. Our respective analysis based on linear regression with model selection leads to the following results:

- The degree to which the dynamics of glucose variation can be predicted from sensor data appears promising.
- Care is needed for avoiding over-fitting of the model to the experimental data. Naïve measures of precision based on an assumption of independence of random deviations lead to extreme over-fitting. However, cross validation using runs as independent observational units leads to a rather simple and plausible model.
- The factor run is needed in the model for obtaining acceptable results. This means that an additive constant needs to be obtained for each run. Considering practical applications for prediction, this means that a baseline adjustment will be needed in practice, i.e., some measurements of the glucose concentration by traditional methods will be needed for each person and probably repeatedly in a regular time pattern to calibrate the model individually.

There are a number of alternative approaches to obtaining a prediction method:

- Since the random deviations $E_{ir}$ are correlated, the methods used for regression between time series should be applied. Note, however, that care must be taken to obtain “predictions” in the sense of regression that are true predictions, i.e., that only rely on past and present values of the explanatory variables. A simple way to implement ideas along this line is to introduce lagged versions of the explanatory variables in the approach discussed in this paper.
- Since the explanatory variables have their own measurement error and sometimes outliers,
filtering and outlier detection may improve the results.

- Instead of Least Squares, robust regression methods, which perform better in the presence of outliers and long-tailed error distributions, can be used to find the model and estimate its parameters.
- We have used transformations of the variables on the bases of general considerations and visual inspection of residual analysis plots. There are more general models which allow for finding suitable transformations automatically, known as General Additive Models (GAM) and Multiple Adaptive Regression Splines (MARS). Limited investigations with these methods did not produce better results in our data set.
- We have summarized the spectra produced by the sensors by averages over extended bands and then using these averages as the explanatory variables in our models. It might pay to estimate a smooth weighting function for the wavelengths to use the information of a spectrum optimally. Such methods are treated by the filed of Functional Data Analysis.

However, the further development of the technology envisions not only improvements in the techniques used to derive a predictive model, but also, the enhancement of other crucial elements of the monitoring platform, such as the attachment of the sensor to the skin and configuration of the sensors. Moreover, the idea of using multiple penetration depths in order to extract the relevant information from the different skin layers is also being further developed.

In a next phase, individual sensors that are currently distributed over the lower and upper arm will be moved closer together, preferably even merged into a single multi-sensor base. The multi-sensor data fusion task will then need to be adapted to this new hardware, and tested to establish whether further improvements can be achieved to move closer towards real-time monitoring of glucose variations in patients with diabetes. It will also need to be further investigated whether a universal data consideration, looking at T1DM (Type 1 Diabetes Mellitus) and T2DM (Type 2 Diabetes Mellitus) is a feasible proposition. Early indications suggest that this may not be the case. As concluded in an earlier work by Caduff et al., model parameters (or models) derived from data of i.v. clamp procedures are not adequate for applications in a closer to daily life situation. Hence in a next trial series, experiments with oral carbohydrate administration will be performed to continue with the development process.

6 References:


