



# Classification of diabetes and measurement of blood glucose concentration noninvasively using near infrared spectroscopy



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## HIGHLIGHTS

- Background and noise of the near infrared spectral data are eliminated by our proposed algorithm simultaneously.
- Nonlinear calibration techniques are used for blood glucose non-invasive measurement *in vivo*.
- The hybrid method is applied to diabetic classification (*in vivo*) and blood glucose concentration measurement (*in vivo*).
- Human tongue is firstly chosen as the measurement site for blood glucose non-invasive measurement in this study.
- LSSVM model with RBF kernel provides a substantial improvement in the prediction accuracy and adaptability.

## ARTICLE INFO

### Article history:

Received 13 May 2014

Available online 15 October 2014

### Keywords:

Classification of diabetes

Blood glucose noninvasive measurement

Near infrared spectroscopy

Wavelet prism

Modified uninformative variable elimination

Least squares support vector machine

## ABSTRACT

Developing noninvasive blood glucose monitoring method is an to immense need to alleviate the pain and suffering of diabetics associated with the frequent pricking of skin for taking blood sample. A hybrid algorithm for multivariate calibration is proposed to improve the prediction performance of classification of diabetes and measurement of blood glucose concentration by near infrared (NIR) spectroscopy noninvasively. The algorithm is based on wavelet prism modified uninformative variable elimination approach (WP-mUVE) combined with least squares support vector machine (LSSVM), named as WP-mUVE-LSSVM. The method is successfully applied to diabetic classification experiment (*in vivo*) and blood glucose concentration measurement experiment (*in vivo*) respectively. Human tongue is selected as the measuring site in this study. To evaluate effectiveness of pretreatment method and quality of calibration models, several usually used pretreatment methods and kernel functions of LSSVM are introduced comparing with our method. Higher quality data is obtained by our pretreatment method owing to the elimination of varying background and noise of spectra data simultaneously. Better prediction accuracy and adaptability are obtained by LSSVM model with radial basis kernel function. The results indicate that WP-mUVE-LSSVM holds promise for the classification of diabetes and measurement of blood glucose concentration noninvasively based on human tongue using NIR spectroscopy.

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## 1. Introduction

Diabetes and its complications (diabetic retinopathy, heart diseases, stroke, neuropathy and birth defects) impose significant economic consequences on individuals, families, health systems, and countries [1,2]. In order to the maintenance of blood glucose level, frequent monitoring of blood glucose and injecting corresponding dosage of insulin are essential parts of diabetic management.

Although most blood glucose monitor is minimally invasive, patients still suffer from the inevitable pain and infection via the finger-tip stick method several times a day [3,4]. Thus, a number of techniques employed for blood glucose noninvasive measurement have been proposed, such as reverse iontophoresis [5,6], thermal emission spectroscopy [7,8], absorbance spectroscopy (including near-infrared (NIR) spectroscopy [9–11] mid-infrared (MIR) spectroscopy [12,13]), photoacoustic spectroscopy [14], Raman spectroscopy [15], fluorescence [16], ultrasound [17], and optical coherence tomography [18].

NIR spectroscopy has become one of the most promising techniques for blood glucose noninvasive measurement with the

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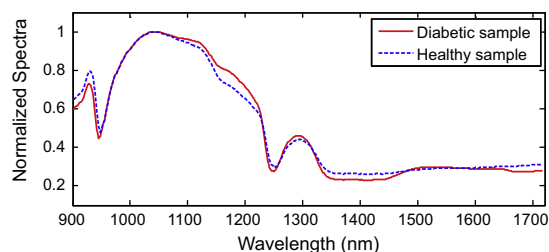


Fig. 1. Spectral comparison between a diabetic sample and a healthy sample.

development of chemometrics. The concept is to irradiate a harmless near-infrared light (750–2500 nm) on a vascular region (1–100 mm deep) of the body and then extract the *in vivo* glucose concentration from the resulting spectral information [19,20]. The basic premise of this technique is that glucose specific information is embedded within near infrared spectra. NIR spectroscopy has been employed to measure glucose in ear lobe, finger, forearm, cheek and so on [21]. Human tongue is chosen as the measurement site for blood glucose noninvasive measurement in this study. One advantage is there is no need to circumvent the individual difference caused by the thickness and thermal properties of the skin as a result that tongue is a muscular structure without skin. Another advantage is that tongue offers high vascularity, little fatty tissue so that it is much easier to get effective blood information than any other regions of the human body. Actually, it has been approved by Burmeister and Arnold [22] that tongue provides spectra with the highest signal-to-noise ratio (SNR) for blood glucose noninvasive measurement among six monitoring sites (including cheek, lower lip, upper lip, nasal septum, tongue, and webbing tissue between the thumb and forefinger) [22]. All those proofs indicated that human tongue could be a possible measurement site for blood glucose noninvasive measurement.

This technique has a limitation that it is sensitive to experimental condition in temperature, humidity, atmospheric pressure and carbon dioxide content. Prediction performance can be seriously degraded when calibration model is established based on the NIR spectra data including uninformative signal. It is well known that removal of the irrelevant information from data before the modeling should improve the final calibration model. Various methods for correcting or removing the background variation have been developed, such as multiplicative scatter correction (MSC), wavelet transform [23], polynomial fitting [24], penalized or weighted least squares [25], and robust local regression. To eliminate the effect of interference variables in the spectra further, variable selection methods such as uninformative variable elimination (UVE) [26], randomization test (RT) [27] and competitive adaptive reweighted sampling (CARS) [28] have been developed. However, those methods are utilized to eliminate either varying background or interference variables. The methods for eliminate varying background and noise of data simultaneously are very few, and among them, only the approach proposed by Chen is successfully applied to simulated spectral data set and experimental NIR spectral data. To the best of our knowledge, no method has been used for blood glucose non-invasive measurement. Besides, high-accuracy quantitative calibration is also a key point to improve the final prediction performance. The most important linear calibration method for spectroscopic data analysis is partial least squares regression (PLSR) [29]. The greatest problem in PLS methodology is that the spectrum property relationship is assumed to be linear. But it is known that this assumption is always unacceptable for systems with strong intermolecular or intramolecular interactions, such as hydrogen bonding. Especially, for the non-invasive measurement of human blood glucose with NIR spectroscopy, the nonfulfillment of the Lambert–Beer Law leads to intrinsic nonlinearity of the sys-

tems, such as the interaction between components, the distribution irregularity of the blood components, and baseline shifts. Hence nonlinear calibration techniques are the essential requirements for building robust calibration models since such calibration techniques have the potential of modeling severe intrinsic nonlinearities that can be found in natural multicomponent systems. Support vector machines (SVMs) [30,31] might be regarded as the perfect candidate for spectral regression purposes. A large advantage of SVM-based techniques is their ability to model nonlinear relationships. However, few researches pay attentions on nonlinear modeling especially in the field of blood glucose non-invasive measurement using NIR spectroscopy.

Therefore, a hybrid method based on wavelet prism modified uninformative variable elimination (WP-mUVE) method and least squares support vector machine (LSSVM), named WP-mUVE-LSSVM, is proposed in this paper. Owing to integrate the advantages of WP-mUVE and LSSVM, this method can not only eliminate varying background and noise of data simultaneously but also has the ability to model nonlinear relationships. The method is successfully applied to two experimental NIR spectra data *in vivo*: one is for classification of diabetes, the other is for measurement of blood glucose concentration. In order to verify effectiveness of the proposed method, several pretreatment methods are employed to compare with WP-mUVE such as first-derivative method (Der1) calculated by the Savitzsky–Golay method, second-derivative method (Der2) calculated by the Savitzsky–Golay method, multiplicative scatter correction (MSC), and orthogonal signal correction (OSC). It is shown that a feasible calibration model is established for classification of diabetes and measurement of blood glucose concentration noninvasively based on human tongue using NIR spectroscopy.

## 2. Theory and algorithm

### 2.1. Wavelet prism modified uninformative variable elimination approach

The wavelet prism modified uninformative variable elimination approach (WP-mUVE) is proposed by Chen [23] to eliminate the varying background and noise simultaneously for multivariate calibration of NIR spectral signals. This method is based on the wavelet multi-resolution technology, WP, introduced by Tan and Brown [32] for eliminating matrix background and high-frequency noise. WP method can split the signal into different frequency components, which retain the original resolution of the signal. Modified uninformative variable elimination (mUVE) is developed from the UVE method, which is proposed by Centner [33,34] to eliminate those clearly uninformative variables by computing the reliability of each variable in the model and retaining only the most informative variables. The contribution of *j*th variable in multivariate calibration determined by the formula:  $t_j = \frac{\text{mean}(b_j)}{\text{std}(b_j)}$ ,  $j = 1, 2, \dots, p$ , where  $\text{mean}(b_j)$  and  $\text{std}(b_j)$  are estimated as a mean and standard deviation from the vector of  $nb_{ij}$  ( $i = 1, 2, \dots, n$ ;  $n$  is the number of samples) regression coefficients obtained by (leave-one-out) jackknifing, and  $p$  is the number of variables. The larger absolute *t*-value is, the more important the corresponding variable is. In conjunction with mUVE criterion, WP-mUVE can be used to remove the low-frequency varying background and the high-frequency noised simultaneously. For more detail description about the WP-mUVE, see Ref. [23].

### 2.2. Least squares support vector machine

Least square support vector machine (LSSVM) is an optimized algorithm based on standard SVM [30,31]. A large advantage of

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