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An automatic glucose monitoring signal denoising method with noise level estimation and responsive filter updating

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ABSTRACT

Although continuous glucose monitoring (CGM) devices have been the crucial part of the artificial pancreas, their success has been discounted by random measurement noise. The difficulty of denoising methods for CGM is that the filter parameters are hard to be determined to well reflect the internal blood glucose dynamics and the real noise level. Besides, the noise level may change from device to device, subject to subject and also within the subject as time goes on which thus requires that the filter parameters should be adjusted to follow the noise changes. In this paper, we proposed an automatic CGM signal denoising method which covers three important components. First, the state transition matrix which reveals the internal blood glucose dynamics and plays an important role in determining filter parameters can be estimated in response to different patients. Second, the real noise level can be estimated which are used to set the values of filter parameters properly. Third, a responsive filter updating rule is developed which can judge whether the values of filter parameters should be updated in response to the variability of signal-to-noise ratio. The process of dealing with the CGM signals is executing as follows: the model parameters and the noise level are evaluated using Expectation Maximization (EM) algorithm which can fix proper filter parameters for the current signals. Then, a confidence interval is defined by computing the power spectral density (PSD) of the CGM signals to identify the changes of noise level which can tell whether or not the parameters of Kalman filter (KF) should be adjusted. The above issues are investigated based on thirty *in silico* subjects and ten clinical subjects. The proposed method can work well to identify the changes of noise level and determine proper filter parameters.

1. Introduction

Diabetes is a global health problem that affects about 387 million people around the world up to 2014 representing 8.3% of the adult population and caused 4.9 million deaths in 2014 [1]. The cost for diabetes in health expenditure was at least USD 612 billion dollars which occupied 11% of total spending on adults in 2014 [2]. Diabetes can cause many complications including heart disease, kidney failure, stroke, foot ulcers and so on [3]. There are two types of the diabetes mellitus: Type 1 diabetes mellitus (T1DM) and Type 2 diabetes mellitus [4]. Insulin therapy is crucial for diabetes patients, since it can help patients to improve their life quality. The ability of monitoring blood glucose has enhanced tremendously thanks to the self-monitoring of blood glucose (SMBG) [5–7]. However, SMBG measurements which typically lead to uncomfortable finger sticking methods are only collected three to four times a day which cannot reflect blood glucose variation of diabetic patients immediately. So the glucose concentration control based on SMBG is usually suboptimal.

Blood glucose measurement techniques can be divided into invasive measurement and non-invasive measurement. A non-invasive blood glucose monitoring system can avoid substantial pain to the patients [8,9], while invasive blood glucose measurement can provide highly accurate readings [10]. In the past few years, the development of the so-called artificial pancreas has helped to maintain glucose concentration within safe ranges for T1DM patients [11]. Continuous glucose monitoring (CGM) devices are one of the key parts of the artificial pancreas and can be regard as a valid alternative to conventional SMBG method [12–15]. CGM devices can sample subcutaneous glucose concentration as frequently as one minute and can store the data for several days. In an

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online application, CGM signals can generate hypo/hyperglycemic alert which will help patients make corrective decisions to prevent severe events immediately [16,17]. Furthermore, CGM data are the input to the artificial pancreas controller which determines the infusion of the insulin. Thus the quality of the CGM data is of great importance for T1DM patients.

Unfortunately, the accuracy and the efficiency of the CGM signals have to be improved [18]. Missing true alert events or generating false alerts depends largely on the reliability of CGM signals. Cobelli et al. [19–21] have pointed out the CGM sensors affected by random noise and calibration error can markedly affects the performance of the abnormal glycemic event alert system. In fact, in order to improve the quality of the CGM signals, the random noise should be removed from the data through the digital filter [19–21]. The purpose of filtering is to obtain the true signals from the measurement signals.

Low-pass filtering is one of the most common methods to remove the noise from the measured signals. One of the disadvantages of low-pass filtering is that it will introduce large delay which distorts the true signals. For alert of abnormal glycemic events, the delayed signals seem to be useless since it cannot generate alarm timely which is of great importance for patients to take corrective action to avoid hyper/hypoglycemia. Medtronic MiniMed used a finite impulse response (FIR) filter whose equation is $\hat{y}_k = a_0 y_k + a_1 y_{k-1} + \cdots + a_M y_{k-M}$ to reduce random noise in Guardian RT where $\hat{y}_k$ is filtered signals and y_k is measured values [22,23]. In practice, a seventh-order filter was in usual used [24]. DexCom used an infinite impulse response filter (IIR) whose equation is described as $\hat{y}_k = -a_1\hat{y}_{k-1} - \cdots - a_N\hat{y}_{k-N} + b_0 y_k + b_1 y_{k-1} + \cdots + b_M y_{k-M}$ in Seven Plus to elaborate the signals [25]. The obvious problems of these methods are that there is no criterion to guide how to determine the proper parameters to deal with the measured signals. Then another method called Kalman filter (KF) was adopted to improve the filter performance. Kalman filter is a common approach using recursive maximum likelihood for state estimation. At first, Bequette [26] used Kalman filter to compensate the blood glucose to subcutaneous glucose transport lag and to predict the future blood glucose. Then KF was used to deal with the CGM data through constructing improved model by Knobbe and Buckingham [27]. However, the filter parameters are fixed once determined which may not reflect the noise variability. In fact, the noise level may change from patient to patient (interindividual variability) and with time even for the same patient (intraindividual variability). Facchinetti and Sparacino et al. [28,29] have noticed these two different kinds of noise changes and first determined KF parameters by estimating the specific noise level. The denoising module has been an important part of the "smart sensor" [20,21] to improve the accuracy and certainty of the CGM sensors. However, their method continuously estimated and updated the filter parameters although the noise level may not change all the time in practice which increases computation complexity and imposes heavy burden. Instead of blind filter parameter updating, it is better to update the KF parameters only when it is necessary. The critical issue is to develop a proper judgment rule which can determine whether the noise level has changed so that the filter parameters should be adjusted. Zhao et al. [30] proposed an automatic denoising method in which the noise level is evaluated using expectation maximization (EM) algorithm which can fix proper filter parameters for the current signals and a confidence interval is defined by computing the power spectral density (PSD) of the CGM signals to tell whether or not the parameters of Kalman filter (KF) should be adjusted.

However, there are still some problems which may need to take careful consideration. First, the state transition matrix which is the internal description of the system is a crucial parameter for KF. In previous denoising methods [28–30], the state transition matrix used for KF was assumed the same for different subjects with T1DM. The unified state transition matrix may not accurately describe different glucose dynamics for different subjects, which may affect the performance of the KF. Second, the confidence interval is defined by arbitrarily setting two adjustable parameters in [30], which cannot accurately capture the changes of noise level. Third, the automatic denoising method [30] is only illustrated based on *in silico* subjects without considering its feasibility for clinical subjects.

In this paper, the previous automatic denoising method [30] is further extended by the authors. We proposed an automatic glucose monitoring signal denoising method with noise level estimation and responsive filter updating. Here, responsive means the filter updating is only made as a reaction to the changes of noise level instead of blind updating. Two important issues are addressed in this paper: (1) How to estimate state transition matrix of the blood glucose for different T1DM individuals? (2) How to properly quantify the confidence interval to check whether the noise level has changed? The contribution of this article (*i.e.*, the difference from previous work [30]) is summarized as below:

(1) The state transition matrix of the filter model is estimated based on EM algorithm, which can reflect the dynamics of blood glucose for different patients, instead of using the fixed parameters.
(2) A proper confidence interval is defined by quantitatively analysing the PSD values of high frequency band signals instead of arbitrarily setting two adjustable parameters.
(3) More illustration results are reported for *in silico* subjects. Besides, the proposed method is applied to ten clinical subjects with enhanced reliability and practicality.

The results show that EM algorithm can estimate the noise level accurately and thus properly determine the filter parameters based on thirty *in silico* subjects and ten clinical subjects. Besides, the responsive filter updating method can significantly reduce the computation burden by avoiding blinding updating. Better filter results are reported by comparing the proposed algorithm with previous methods.

2. Preliminary

2.1. The conventional Kalman filter

The Kalman filter has always been regarded as an optimal method to filter and predict data for its simplicity. For digital filters, if we consider a discrete homogeneous case, we will obtain the following model system equation and the measurement equation

$$\mathbf{x}(k+1) = \mathbf{A}\mathbf{x}(k) + \mathbf{w}(k) \quad (1)$$

$$\mathbf{y}(k) = \mathbf{C}x(k) + \mathbf{v}(k) \quad (2)$$

where $\mathbf{x}(k)$ is the state vector of the process at time k, $\mathbf{A}$ is the state transition matrix of the process, $\mathbf{w}(k)$ is the process noise vector, usually a zero-mean white Gaussian noise associated with unknown covariance matrix $\mathbf{Q}$, $\mathbf{y}(k)$ is the measurement of $\mathbf{x}(k)$ at time k, $\mathbf{C}$ is a connected matrix between the process vector and the measurement vector, $\mathbf{v}(k)$ is a zero-mean white Gaussian measurement noise with unknown covariance matrix $\mathbf{R}$.

In order to estimate state vector $\mathbf{x}(k)$ from the measurement vector $\mathbf{y}(k)$, the KF filter is implemented as below

$$\mathbf{x}_k^{k-1} = \mathbf{A}\mathbf{x}_{k-1}^{k-1} \quad (3)$$

$$\mathbf{P}_k^{k-1} = \mathbf{A}\mathbf{P}_{k-1}^{k-1}\mathbf{A}^T + \mathbf{Q} \quad (4)$$

$$\mathbf{K}_k = \mathbf{P}_k^{k-1}\mathbf{C}^{\mathrm{T}}(\mathbf{C}\mathbf{P}_k^{k-1}\mathbf{C}^{\mathrm{T}} + \mathbf{R})^{-1} \quad (5)$$