An Automatic Denoising Method with Estimation of Noise Level and Detection of Noise Variability in Continuous Glucose Monitoring

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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 real noise level. Besides, the noise level may show both intra-individual and inter-individual variability which thus requires that the filter parameters should be adjusted to follow the noise changes. In this paper, we proposed an automatic denoising method which covers two important components. On the one hand, the noise level can be estimated so that the filter parameters are determined properly. On the other hand, the variability of signal-to-noise ratio can be detected for self-adjustment of filter parameters. First, the noise level is evaluated using a spectral density (PSD) expectation maximization algorithm which can fix proper filter parameters for the current signals. Second, 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. The proposed method can work well to identify the changes of noise level and determine proper filter parameters.

Keywords: Signal denoising; Kalman filter; Expectation Maximization (EM); noise variability; power spectral density (PSD); Type 1 diabetes mellitus (T1DM)

1. INTRODUCTION

Diabetes is a global health problem that affects about 387 million people around the world in 2014 (Shi et al. 2014). Type 1 diabetes mellitus (T1DM) is one of the diabetes resulting from an absolute deficiency of insulin secretion (American Diabetes Association 2014). Therefore T1DM patients cannot maintain their blood glucose within a normal range without proper therapeutic protocol. 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 (Cobelli et al. 2011). Continuous glucose monitoring (CGM) devices are one of the key parts of the artificial pancreas. In a real-time application, CGM signals can generate hypo/hyperglycemic alert by comparing the measured glucose concentration with the normal range thresholds. Unfortunately, the CGM sensors are affected by random noise which markedly affects the performance of the abnormal glycemic event alert system, and the efficiency of controllers embedded within artificial pancreas. 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.

However, there is relatively limited literature on denoising methods for CGM signals. Medtronic MiniMed used a finite impulse response (FIR) filter in Guardian RT to reduce random noise (Steil et al. 2003) while DexCom used a digital infinite impulse response filter (IIR) in Seven Plus to elaborate the signals (Brauer et al. 2005). Then another method called Kalman filter (KF) was adopted to improve the filter performance (Bequette et al. 2004). The obvious problems of these methods are that there is no criterion to guide how to determine the proper parameters to well reflect the noise level. Besides, the filter parameters are fixed once determined which may not reflect the noise variability. Facchinetti and Sparacino continuously tuned the filter parameters realtime by a stochastically Bayesian smoothing criterion (Facchinetti et al. 2011) and then they proposed a real-time algorithm to improve CGM sensors certainty and accuracy (Facchinetti et al. 2013a,b). However, for denoising method, it cannot automatically judge when the noise level has changed and whether the filter parameters should be adjusted. Instead, they used a sliding window of fixed integer $N$ to update the parameters consecutively online no matter whether the noise level is changed or not.

In this paper, we mainly focus on measurement noise to show our method better than previous method in filtering process. In order to achieve good filter performance, two important questions should be answered. One is how to reveal the noise level and thus determine the proper filter parameters; and the other is how to judge the changes of noise level so as to revise filter parameters to be adaptive to the changes. In order to solve the above mentioned problems, we proposed an online automatic denoising method consisting of two components. We use Expectation Maximization (EM) algorithm (Mader et al. 2014) to estimate the noise level of the CGM signals which can be used to determine the KF parameters for the current signals. Then we analyze power
spectral density (PSD) of the CGM signals in high frequency band filtered by a high-pass filter to judge whether or not the level of the noise has changed and the parameters of the filter should be updated. The results show that EM algorithm can estimate the noise level accurately and thus properly determine the filter parameters. Besides, the automatic detection method can promptly identify the changes of noise level and thus update the parameters of the KF. Better filter results are reported by comparing the proposed algorithm with previous methods.

2. The Conventional Kalman Filter

For digital filters, if we consider a discrete homogeneous case, we will obtain the following model system equation and the measurement equation

\[ x(k+1) = Ax(k) + w(k) \]  
\[ y(k) = Cx(k) + v(k) \]

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

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

\[ x_k^{k-1} = Ax_k^{k-1} \]  
\[ P_k^{k-1} = AP_k^{k-1}A^T + Q \]  
\[ K_k = P_k^{k-1}C^T (CP_k^{k-1}C^T + R)^{-1} \]  
\[ x_k = x_k^{k-1} + K_k (y_k - Cx_k^{k-1}) \]  
\[ P_k = P_k^{k-1} - K_kCP_k^{k-1} \]

where \( x_k^{k-1} \) is predicted estimation of \( x(k) \) at time \( k-1 \), \( P_k^{k-1} \) is the covariance matrix of the predicted estimation error, \( x_k \) is the filtered value of \( x(k) \) at time \( k \), \( P_k \) is the covariance matrix of the filter error, \( K_k \) is the Kalman gain, and \( x_0^0 \) and \( P_0^0 \) are the initial conditions.

For KF, the covariance matrix \( Q \) and \( R \) are two important indices which in fact reveal the noise level in real application. Therefore, the two indices should be well estimated to determine KF parameters. However, they are in general set subjectively and kept invariable for different cases. Therefore, the corresponding KF parameters cannot work well to denoise CGM signals because the noise level may be quite different for different patients and even for the same subject.

3. Methodology

In this section, we will introduce how to use EM method to estimate the noise level of the CGM signals, and then we will explain the automatic detection method by analysing PSD to judge the variability of the CGM data which determines whether or not to update the parameters of the filter.

3.1 Filter Parameter Estimation by Evaluating Noise Level

In the present work, the KF is used to denoise the CGM signals. Therefore, the parameter estimation is performed based on KF. First, the glucose value \( u(k) \) can be described as a double integrated random walk model (De Nicolao et al. 1997)

\[ u(k) = 2u(k-1) - u(k-2) + w_k(k) \]

where \( w_k(k) \) is a zero-mean white Gaussian noise with variance \( \lambda^2 \).

Let \( x_1(k) = u(k) \), \( x_2(k) = u(k-1) \), \( x(k) = [x_1(k) \ x_2(k)]^T \), then the state transition matrix is given by \( A = \begin{bmatrix} 2 & -1 \\ 1 & 0 \end{bmatrix} \) based on (1). The measurement \( y(k) \) in (2) is a scalar, so that we can get that \( C = [1 \ 0] \). The process noise vector \( w(k) \) and the measurement vector \( v(k) \) are modelled as a zero-mean white Gaussian noise (Cescon et al. 2014), so the covariance matrix \( Q \) and \( R \) are then calculated as \( Q = \begin{bmatrix} \lambda^2 & 0 \\ 0 & \sigma^2 \end{bmatrix}, \ R = \sigma^2 \). If \( \lambda^2 \) and \( \sigma^2 \) are determined, we can use Kalman filter to denoise the CGM signals. Therefore, the key issue is to estimate the two parameters which are quite relevant with the noise level.

Here, we adopt Expectation Maximization (EM) algorithm (Shumway et al. 1982) to estimate the covariance matrix \( Q \) and \( R \). EM algorithm has been successfully applied for parameter estimation. However, it has not been used for estimation of noise level in CGM signals. It is an iterative method for obtaining maximum likelihood estimates of parameters in statistical models especially when the observations are regarded to be incomplete data. For CGM signals, the state vector \( x(k) \) in (1) are in fact unobserved data, so EM algorithm is suitable to handle the parameter estimation of filter for CGM denoising.

The \( n \)-size CGM signals are chosen to estimate the parameters. Assume the initial value \( x(0) \) is a random vector with mean vector \( \mu \). The noise level is estimated and the filter parameters are then determined by the following steps.

1) Calculate \( x_1^0, P_1^0, P_1^{k-1} \) in equations (3)-(7) with initial value \( \mu(0) \), \( Q(0) \) and \( R(0) \) for \( k=1,2,\ldots,n \) with \( x_0^0 = \mu(0) \)
2) Calculate \( x_n^k, P_n^k, P_{n,k}^N \) in equations (9)-(12) for \( k = n, n-1, \ldots, 1 \):

\[
J_{k+1} = P_{k+1}^{-1}A^T(P_{k+1}^{n-1})^{-1} \tag{9}
\]

\[
x_n^k = x_n^{k-1} + J_{k+1}(x_n^k - A x_n^{k-1}) \tag{10}
\]

\[
P_n^k = P_{n,k}^N + J_{k+1}(P_n^k - P_{n,k}^{-1})J_{k+1}^T \tag{11}
\]

where

\[
x_n^k = E(x_n^k | y_1, y_2, \ldots, y_n)
\]

\[
P_n^k = E[(x_n^k - x_n^k)(x_n^k - x_n^k)^T | y_1, y_2, \ldots, y_n]
\]

Then calculate \( P_{n,k-1}^N \) for \( k = n, n-1, \ldots, 1 \):

\[
P_{n,k-1}^N = P_{n,k}^N J_{k+1}^T + J_{k+1}(P_{n,k-1}^N - A P_{n,k}^{-1})J_{k+1}^T \tag{12}
\]

where

\[
P_{n,k}^N = (I - KC)AP_{n,k}^{-1}
\]

3) Calculate \( \mu(t), Q(t) \) and \( R(t) \) in equations (13)-(18):

\[
\mu(t+1) = x_n^k \tag{13}
\]

\[
Q(t+1) = \frac{(W - VU^{-1}V^T)}{n} \tag{14}
\]

\[
R(t+1) = \frac{\sum_{k=1}^n [(y_k^* - Cx_n^k)(y_k - Cx_n^k)^T + CP_n^kC]}{n} \tag{15}
\]

\[
U = \sum_{k=1}^n (P_{n,k-1}^N + x_n^k(x_n^k)^T) \tag{16}
\]

\[
V = \sum_{k=1}^n (P_{n,k}^N + x_n^k(x_n^k)^T) \tag{17}
\]

\[
W = \sum_{k=1}^n (P_n^k + x_n^k(x_n^k)^T) \tag{18}
\]

4) Repeat step 1) to 3) until the value of \( Q, R \) and the log likelihood function are stable:

\[
\log L = -0.5 \cdot \left( \sum_{k=1}^N \| C P_{k-1}^{-1}C^T + R \| + \sum_{k=1}^N (y_k^* - Cx_n^{k-1})^T (C P_{k-1}^{-1}C^T + R)^{-1} (y_k^* - Cx_n^{k-1}) \right) \tag{19}
\]

By the above steps, we can get the estimation of the covariance matrix \( Q \) of process noise and the covariance matrix \( R \) of measurement noise. They reveal the noise level of the current signals. Then the CGM signals are filtered by KF using (3)-(7).

### 3.2 Automatic Detection of Noise Variability

In order to deal with the variability of the noise along time direction, an online automatic detection method is proposed which can judge whether or not the noise of the CGM has changed. It is developed based on analysis of energy of signals in high frequency band.

The frequency bands of the glucose signals can summarize the overall dynamic characteristics of the blood glucose since different physiological mechanisms can drive different frequency bands. The energy spectrum of blood glucose signals in the individuals without diabetes can be divided into four major frequency bands (Rahaghi et al. 2008 and Zhao et al. 2013, 2014). They claimed that the first frequency band, covering approximately 5 to 15 min (Band I), contains very little energy of all of the system. Because the T1DM patients cannot produce enough insulin caused by the destruction of the pancreatic beta-cells, the dynamics of Band I are absent in the glucose signals (Gough et al. 2003). In fact, the frequencies in Band I are deemed to be consist of measurement noise without any significant dynamic characteristic of the glucose for CGM signals (Lu et al. 2010).

It means the information in high frequency band can be used to define the confidence limit. Based on the predefined confidence interval, the noise variability of CGM signals will be detected online where a sliding window is used along time direction to check the changes of noise. It is implemented in the following procedure:

1) At time \( t \), the \( N \)-size CGM signals are filtered by a high-pass filter in which the cut-off frequency is 15 min. Here, \( N \) denotes the length of sliding window. The signals in high-frequency band are deemed to be noises which will be used to determine the initial confidence interval of noise level.

2) Adopt the Welch’s method with 50% overlapped Hamming window to estimate the power spectral density (PSD) of the signals in high-frequency band. Then the confidence interval is determined by \( [n_p, n_t, p] \) where \( n_p \) and \( n_t \) are adjustable parameters; and \( p \) denotes the PSD value.

3) Perform high-pass filter on the new samples in a sliding window of \( N \)-size and calculate their PSD value as shown in Steps 1) and 2). Compare the new PSD against the predefined confidence interval. If there are three consecutive PSD values outside this interval, it means that the noise level has changed. Then the filter parameters should be adjusted to follow this change. Otherwise, use previous filter parameter to denoise the current CGM signals.

4) To update the parameters of KF, find the first sliding window that shows a PSD value going out of the confidence interval. It is then used to estimate the new parameters by applying the EM algorithm described before. And the confidence interval is reset using the new PSD values.

Figure 1 explains the procedure of the automatic denoising method of noise variability.
4. SIMULATION AND DISCUSSION

4.1 Database

Simulated data are created by FDA-accepted University of Virginia/University of Padova (UVA/Padova) T1DMS Type 1 Diabetes Metabolic Simulator version 3.2 with 5 min as sampling interval. In order to simulate daily life, the simulation is processed open-loop without any adjustments for the regulation of schedule. Three meals for breakfast, lunch, and dinner are taken at 7:00, 12:00, and 18:00 with 40g, 85g and 60g CHO's, respectively for each subject. Bolus insulin is given simultaneously with CHO's and the ratio of the meal bolus and the meal amount is set to be optimal. Thirty in silico subjects are used which include ten adolescent, ten adult and ten children with five days simulation data.

Because our method is mainly focus on filtering the measurement noise, the noisy CGM signals are generated by adding to the blood glucose (noise-free) signals a zero-mean white Gaussian noise sequence with standard deviation 2mg/dl, 3mg/dl, 4mg/dl and 5mg/dl respectively (Facchinetti et al. 2011). The simulation data of the first day is considered to be the tuning interval to estimate the process noise covariance and the measurement noise covariance by EM algorithm, and then we use KF with estimated parameters to deal with CGM signals of the following four days.

4.2 Results and discussions

Here, the proposed Kalman filter based on EM algorithm is compared with two methods, the Kalman filter proposed by Facchinetti et al.(2011) and moving average (MA) filter adopted in CGM commercial devices (Mastrototaro et al. 2002) whose filter equation is described as

\[ \hat{x}(k) = c_1 x(k) + c_2 x(k-1) + \ldots + c_M x(k-M+1), \]

where \( M \) is the order and \( c_i \) is the weight coefficient. Here, \( M = 7 \) and \( c_i = 0.65^i \).

In order to value the performance of the filter, two metrics are used: Root-mean-square error (RMSE (mg/dl)) and Time lag (TL) (Facchinetti et al. 2011).

Table 1 summarizes the filtering results using three different methods for thirty in silico subjects. For convenience, Facchinetti denotes the KF method proposed by Facchinetti et al. 2011 in the table. It is obvious that KF based on EM is significantly better than the other two methods as evaluated by RMSE and Time Lag. For RMSE, the accuracy of KF based on EM is significantly better than that of the other two methods based on paired-t test (Montgomery and Runger, 2006) for all noise levels. For Time Lag, the KF based on EM is always zero for different noise levels. The parameters \( t \) in (21) is only integer, so Time Lag equals to zero does not mean there is no time delay, actually it means time delay less than 1 samples(5 minutes). In fact, the results in Table 1 also show that the performance of the Kalman filter based on stochastically smoothing criterion (Facchinetti et al. 2011) is similar with that of the MA algorithm with the increase of standard deviation of noises. Figure 2 shows the filtering results of CGM signals using three different methods for Subject #5 in comparison with the real noise-free signals denoted by BG. KF by using EM denotes the proposed algorithm, KF by Facchinetti denotes the KF developed by Facchinetti et al. It is clear that the proposed algorithm (KF by using EM) shows better performance in comparison with KF by Facchinetti during peaks of waves of CGM signals. Also, the details in some time interval are zoomed in as shown in Figure 3. MA presents time delay to some extent and the filtered signals by the proposed algorithm are more close to the noise-free values.

In order to simulate the noisy CGM signals, here we add a zero mean white Gaussian noise with varying standard deviation \( \sigma \) to the blood glucose signals of one day where \( \sigma \) is a sinusoidal shape with minimum and maximum values equal to 1 and 5 mg/dl. We use three versions of KF to deal with these noisy CGM signals. First, the samples of the first six hours, i.e. 72 samples, are used to estimate parameters of KF by EM algorithm and then denoise the left CGM signals without updating parameters. It means the parameters of KF are fixed. Second, the proposed automatic detection method is applied to identify the noise variability and determine whether or not the parameters should update. Here, \( N = 72 \), \( n_1 = 0.5 \) and \( n_2 = 1.5 \), which are set by trial and error. Third, the parameters of KF are consecutively updated with a sliding window with length \( N = 72 \). For this method, the parameters are updated using sliding window no matter whether the noise level is changing or not. For \( t > N \), \( N \)-size vector \( y_{ic} = [ y(t-N+1), y(t-N+2) \ldots y(t) ] \) is chosen to update parameters for online application. The length of \( y_{ic} \) is...
fixed and the interval is moved along time direction to obtain the newest noise information as time goes on. For the proposed automatic detection algorithm, the noise variability is then evaluated by PSD and used to indicate whether the filter parameters should be updated.

Table 2 summarizes the filtering results of three different versions of KF based on EM algorithm for thirty in silico subjects. The results reveal that the method with fixed parameters may lead to the suboptimal results which is significantly inferior to the other two methods as evaluated by RMSE and Time Lag. Since the first method does not update the parameters, it takes the least computation time to deal with the signals. However it cannot detect the variability of the noise and the filter results is usually suboptimal. For the last two versions of KF, there is not much difference in the results. The proposed algorithm with automatic detection of noise variability takes much less computation time than the method that updates parameters consecutively without judgement. It is noted that the method that updates parameters consecutively can be regarded as one particular case of the proposed automatic detection method in which \( n_1 = 1 \) and \( n_2 = 1 \). It is not necessary to re-estimate and update the filter parameters if the noise level does not change significantly. The automatic detection method provides a way to evaluate the significance of noise variability and determine whether or not to update the parameters of KF. Figure 4 shows the filtering results of CGM signals using three different versions of KF for Subject #3 in comparison with the real noise-free signals denoted by BG. The signals covering samples 1 through 72 are used to detect the noise variability and define the initial confidence interval for the proposed algorithm. Also, the details in some time interval are zoomed in as shown in Figure 5. It is clear that the filtered signals using filter with fixed parameters is inferior to the other methods since it presents a larger time delay.

5. CONCLUSIONS

In the present work, we propose an online estimation of noise level and automatic detection of noise variability for online CGM denoising. Proper filter parameters are automatically determined based on the estimation of noise level. In comparison with the existing methods, our method has better performance as evaluated by RMSE and Time Lag. Besides, a rational filter parameter self-adjustment is implemented in which the filter parameters can be automatically adjusted only when the noise level has changed instead of blind consecutive updating. The feasibility of the proposed algorithm has been verified based on in silico subjects. It demands less computation time and presents improved denoising accuracy.
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REFERENCES

American Diabetes Association (2014). Diagnosis and classification of diabetes mellitus. Diabetes Care, 37(Supplement 1), S81-S90.


Table 1. The filtering results using three different methods for thirty in silico subjects (mean ± standard deviation)

<table>
<thead>
<tr>
<th>Noise level (Standard deviation(mg/dl))</th>
<th>RMSE(mg/dl)</th>
<th>TL(min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EM</td>
<td>Facchinetti</td>
</tr>
<tr>
<td>2</td>
<td>1.70±0.08</td>
<td>3.53±0.86</td>
</tr>
<tr>
<td>3</td>
<td>2.44±0.16</td>
<td>4.04±1.06</td>
</tr>
<tr>
<td>4</td>
<td>3.15±0.16</td>
<td>5.03±1.21</td>
</tr>
<tr>
<td>5</td>
<td>3.77±0.24</td>
<td>5.59±1.21</td>
</tr>
</tbody>
</table>

Table 2. The filtering results using different EM methods for thirty in silico subjects (mean ± standard deviation)

<table>
<thead>
<tr>
<th>Methods</th>
<th>Metrics</th>
<th>KF with fixed parameters</th>
<th>Automatic detection method</th>
<th>KF with consecutive parameter updating</th>
</tr>
</thead>
<tbody>
<tr>
<td>RMSE(mg/dl)</td>
<td></td>
<td>3.89±1.45</td>
<td>3.39±0.84</td>
<td>3.39±0.84</td>
</tr>
<tr>
<td>TL(min)</td>
<td></td>
<td>0.33±1.27</td>
<td>0.33±1.27</td>
<td>0.33±1.27</td>
</tr>
<tr>
<td>Computation Time(s)</td>
<td></td>
<td>31.70±24.50</td>
<td>839.36±293.64</td>
<td>839.36±293.64</td>
</tr>
</tbody>
</table>