Online Denoising Method to Handle Intraindividual Variability of Signal-to-Noise Ratio in Continuous Glucose Monitoring

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Andrea Facchinetti, Giovanni Sparacino, and Claudio Cobelli*, *Fellow, IEEE*

***Abstract*—In the last decade, the availability of new minimally invasive subcutaneous sensors for monitoring glucose level continuously stimulated research on new online strategies for improving the treatment of diabetes, including hyper/hypoglycemic alert generators and artificial pancreas. An important aspect that has to be dealt with in these applications is the random measurement noise that affects continuous glucose monitoring (CGM) signals. One major difficulty is that for a given sensor technology, the signal-to-noise ratio (SNR) can vary from subject to subject (interindividual variability) and also within subject (intraindividual variability). Recently, a denoising approach implemented through a Kalman filter with parameters automatically tuned, once for all, in a burn-in interval was proposed to cope with the interindividual variability of SNR. In this paper, we propose a new denoising method able to cope also with the intraindividual variability of the SNR. The method resorts to a Bayesian smoothing procedure that uses a statistically-based criterion to determine, and continuously update, filter parameters in real time. The performance of the method is assessed on both Monte Carlo simulation and 24 real CGM time series obtained with the Glucoday system (Menarini, Florence, Italy). The method has a general applicability, also outside from the CGM context.**

***Index Terms*—Alert, diabetes, digital filtering, time series.**

I. Introduction

THE daily management of diabetes, based on diet, physical exercise, and drug administration, can be significantly improved by new minimally invasive portable sensors [1]–[4], which, for several days (e.g., up to two weeks), are able to provide real-time readings of glucose concentration at rates frequent enough (e.g., 1–5 min) to return a "quasi-continuous" profile. For this reason, these devices are commonly referred to as "continuous" [5], in contrast to glucose meters that are commonly employed by patients through 3–4 finger pricks per day. In recent years, continuous glucose monitoring (CGM) data were found to be useful for retrospective analysis, e.g., to optimize insulin dosages by analyzing offline glucose fluctuations [5], [6]. Real-time applications can be even more attractive. For instance, CGM signals are a key component of the so-called artificial pancreas, a device conceived for Type 1 diabetic patients aimed at maintaining glucose concentration within safe ranges by infusing insulin subcutaneously via a pump under the control of a closed-loop algorithm (see [7] and [8] for two recent reviews). Another important online application of CGM sensors is the generation of alerts when glucose concentration is predicted to exceed the normal range thresholds [9]–[15].

However, online applications of CGM sensors are made difficult by the fact that both accuracy and precision of glucose readings are affected by the presence of different sources of error [15], [16], e.g., related to device physics, chemistry, and electronics. As far as accuracy is concerned, the literature is rather large, see, e.g., [17], [18], with the most common approach based on the comparison of CGM readings and reference blood glucose (BG) samples collected in parallel by some gold standard laboratory techniques. This is not without difficulties, because CGM measurements are collected in a site different from the blood, i.e., interstitial fluid [19], and, in addition, BG references are, in the richer protocols, available at 30-min sampling. As far as sensor precision is concerned, it is well established in the literature that CGM time series are also corrupted by a random noise component [16], [20] which complicates signal interpretation and, in particular, may significantly deteriorate the performance of hypo/hyperglycemic alert generation systems [14], [15] as well as that of the controllers embedded within artificial pancreas algorithms [7], [8]. However, characterization of sensor random noise is relatively unexplored. To the best of our knowledge, only two works have partially addressed this issue. In [20], the sensor random noise was modeled in the simplest way, i.e., with a random white noise Gaussian process with a constant-in-time coefficient of variation arbitrarily chosen by the user. In [21], an autoregressive model was proposed to describe a combined sensor noise plus physiological modeling error.

This study deals with the precision of CGM signals. In fact, the quality of CGM signals can be significantly improved by reducing the power of the random noise component through a digital filter placed in cascade to the CGM sensor. In the rest of this paper, this process will be called "denoising."

The literature on denoising approaches for CGM time series is also relatively limited. Some denoising approaches can be found in patents held by CGM manufacturers, even if details are difficult to recover in full. Examples are the finite-impulse response filter used by Guardian RT (Medtronic Minimed, Inc.,

Manuscript received March 8, 2011; revised May 31, 2011; accepted June 21, 2011. Date of publication June 30, 2011; date of current version August 19, 2011. The algorithm proposed in Section II is part of a patent request (WO/2009/136372) deposited by the University of Padova. *Asterisk indicates the corresponding author*.

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Digital Object Identifier 10.1109/TBME.2011.2161083

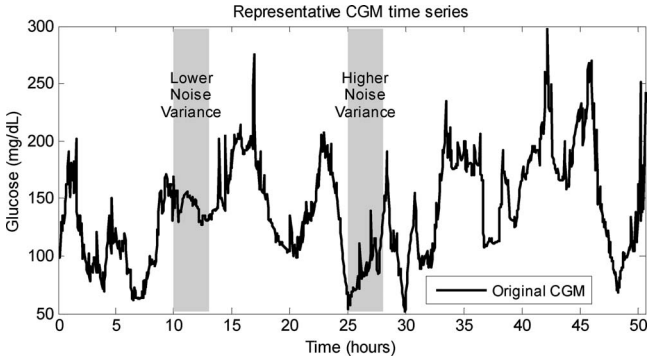

Fig. 1. Representative CGM time series (black line) obtained with the Menarini Glucoday system and taken from [27]. Time intervals 10–13 h and 25–28 h (gray areas) show two situations of lower and higher noise variance, respectively.

Northridge, CA) [9], [22], and the infinite-impulse response filter used by Seven Plus (DexCom, Inc., San Diego, CA) [23]. In [24], a Kalman approach was proposed for glucose prediction which, as a by-product, returns also a denoised CGM profile. The main problem with these strategies is that they all implement filters with fixed parameters. This make them unsuited to cope with the variability of the signal-to-noise ratio (SNR) that CGM signals exhibit within a subject (intraindividual variability) as well as among subjects (interindividual variability) [16].

In the signal-processing literature, several adaptive techniques are suitable to cope with the variability of SNR, for instance, Kalman filtering, algorithms based on recursive least squares, and frequency domain adaptive filters (see [25] and [26] for comprehensive books). In the specific CGM processing area, the interindividual variability of SNR has been recently tackled by a stochastic denoising approach based on a causal Kalman filter (KF), whose parameters are automatically tuned, once for all, in a burn-in interval [16]. However, if the SNR changes during the monitoring (intraindividual variability), the smoothing performed by the denoising approach of [16], below labeled, for sake of reasoning, as KF, will result suboptimal, with portion of the signal which may result under or oversmoothed (see Fig. 6 in Section IV later in this paper). The existence of the intraindividual variability of the SNR is rather visible on the representative CGM time series, obtained with the Menarini Glucoday system and taken from [27], displayed in Fig. 1. As one can note by eye inspection, the noise component in the time interval 25–28 h is greater than in 10–13 h. Therefore, different filtering would be needed for denoising these two portions of the same signal. To the best of our knowledge, denoising approaches able to deal with the intraindividual variability of the SNR are not available in the CGM literature. Incidentally, one can note that some occasional and spurious spikes are also present in the profile of Fig. 1. Given the physicochemical basis of the Menarini Glucoday sensor, these spikes are, in all likelihood, due to episodic occlusions of the microdialysis tube inserted into the abdominal wall caused by particular movements of the patient [28].

In this paper, we propose a new method that is able to face in real time the intraindividual variability of the SNR of CGM signals. The method resorts to a Bayesian smoothing approach and is implemented by a numerically efficient algorithm. The performance of the new method and its superiority to the method of [16] (which is able to deal with the interindividual variability of the SNR only) is assessed both on Monte Carlo simulation and on 24 real CGM time series obtained with the Menarini Glucoday system. The method has a general applicability, also outside from the CGM context.

II. Method

Let us consider, in a discrete-time setting, the problem of estimating the glucose value at the generic sampling time t, denoted as $u(t)$, from data $y(t)$, measured by the CGM sensor, available at times till t, and modeled as

$$y(t) = u(t) + v(t) \tag{1}$$

where $v(t)$ is the measurement error. In (1), the measurement noise is assumed uncorrelated from the useful signal, with zero mean and unknown variance equal to $\sigma^2(t)$ which may vary with t.

In a Bayesian context, estimating $u(t)$ from all the samples $y(t)$ till time t requires an *a priori* model of the autocovariance of $u(t)$. Here, as already done in [16], we describe the expected regularity of $u(t)$ by using a double integration of a white noise process, the so-called integrated random walk model

$$u(t) = 2u(t-1) - u(t-2) + w(t) \tag{2}$$

where $w(t)$ is a zero mean white Gaussian noise with (unknown) variance equal to $\lambda^2(t)$. Multiple-integrated white noise models are particular autoregressive models that are widely used in filtering/smoothing/deconvolution of biomedical signals when the only *a priori* information on the unknown signal is its qualitative regularity [25], [29]–[33]. In fact, this class of models has the advantage over other autoregressive moving average structures of having only one unknown parameter (the variance of the white noise which drives the model), which can be estimated from the data through a smoothing criterion. In (2), the choice of using two integrators (rather than one, three, or four) emerges from a simulation study performed in [16] exploiting a cross-validation strategy. Having fixed a suitable integer N (some tens), for $t > N$ let us define the N-size vectors $\mathbf{y} = [y(t-N+1)\ y(t-N+2) \dots y(t)]$, $\mathbf{u} = [u(t-N+1)\ u(t-N+2) \dots u(t)]$, and $\mathbf{v} = [v(t-N+1)\ v(t-N+2) \dots v(t)]$. Let us also consider the covariance matrix of $\mathbf{v}$ depending on the scale factor σ^2, i.e., $\mathbf{\Sigma_v} = \sigma^2\mathbf{B}$, with $\mathbf{B}$-squared N-size positive-definite matrix expressing our prior knowledge on the structure of the autocorrelation of $\mathbf{v}$. The estimate $\hat{\mathbf{u}}$ is given by

$$\hat{\mathbf{u}} = \left(\mathbf{B}^{-1} + \gamma \mathbf{L}^T\mathbf{L}\right)^{-1}\mathbf{B}^{-1}\mathbf{y} \tag{3}$$

where $\mathbf{L}$ is a squared N-size lower triangular Toeplitz matrix with first column equal to $[1, -2, 1, 0, \dots, 0]^T$. The estimate of (3) can be interpreted as the linear minimum variance estimator of $\mathbf{u}$ given $\mathbf{y}$. Under Gaussianity assumptions, this linear estimator is optimal in broad sense. In (3), γ is given by the ratio σ^2/λ^2 where, for simplicity of notation, the dependence on t has been dropped. Both σ^2 and λ^2 are unknown and, accordingly to the maximum likelihood regularization criterion suggested by De Nicolao *et al.* [30], an "average" γ on the considered window

can be determined by solving (3) for several trial values of γ until the following equation is satisfied:

$$\frac{\mathrm{WRSS}(\gamma)}{N - q(\gamma)} = \gamma \frac{\mathrm{WESS}(\gamma)}{q(\gamma)} \tag{4}$$

where $\mathrm{WRSS}(\gamma) = (\mathbf{y} - \hat{\mathbf{u}})^T \mathbf{B}^{-1} (\mathbf{y} - \hat{\mathbf{u}})$, $\mathrm{WESS}(\gamma) = \hat{\mathbf{u}}^T \mathbf{L}^T \mathbf{L} \hat{\mathbf{u}}$, and $\mathrm{q}(\gamma) = \mathrm{trace}[\mathbf{B}^{-1/2}(\mathbf{B}^{-1} + \gamma \mathbf{L}^T \mathbf{L})^{-1} \mathbf{B}^{-1/2}]$. Once γ is obtained, σ^2 and λ^2 can be estimated. In particular, an estimate of the noise variance valid for time t is given by

$$\hat{\sigma}^2 = \frac{\mathrm{WRSS}(\gamma)}{N - q(\gamma)}. \tag{5}$$

Exploiting the Bayesian embedding, the covariance matrix of the estimation error $\tilde{\mathbf{u}} = \mathbf{u} - \hat{\mathbf{u}}$ can be computed as

$$\mathbf{cov}(\tilde{\mathbf{u}}) = \hat{\sigma}^2 \left(\mathbf{B}^{-1} + \gamma \mathbf{L}^T \mathbf{L} \right)^{-1} \tag{6}$$

whose square-root diagonal elements could be used to estimate the confidence interval of the denoised glucose readings. The computation of $\hat{u}(t)$ and its standard deviation requires $O(N^3)$ operations, where N is the size of the time window in which the smoothing is performed, by exploiting a singular value decomposition based diagonalization procedure discussed in detail in [30]. This computational demand is acceptable for real-time implementation even if is higher than the $O(N)$ required by the KF of method [16] which, however, is not able to deal with the intraindividual SNR variability.

In an online setting, the procedure of (3)–(6) is then repeated at time $t + 1$, $t + 2, \ldots$, with the N-size vector $\mathbf{y}$, $\mathbf{u}$, and $\mathbf{v}$ referred to a sliding temporal window of length N. Obviously, in practical applications, N determines also the length of a burn-in interval where no filtered data can be provided.

Remark 1: Since no information on Menarini Glucoday noise characterization is available, we assume the measurement noise $v(t)$ of (1) to be white and Gaussian. This implies $\mathbf{B} = \mathbf{I}_N$, where $\mathbf{I}_N$ is an N-size identity matrix. In any case, the method we propose is general and flexible to these assumptions. In fact, Gaussanity is not strictly required because it simply ensures the global optimality of the estimator in (3). In addition, a suitable modification of the structure of $\mathbf{B}$ can be used to properly describe correlated noise, e.g., autoregressive, should evidence of this become available for this or other sensors.

In the next sections, we will apply the new method first on a Monte Carlo simulation, then on a real dataset, and we will compare these results with ones provided by the KF of [16]. KF was chosen because, to the best of our knowledge, it is the most sophisticated CGM denoising approach presented in the literature so far, and in particular, demonstrated to be superior to approaches where, in a given subject, a filter with fixed structured parameters (e.g., moving average) is used (see [16] for a quantitative analysis).

III. Assessment on Monte Carlo Simulation

A. Data

In order to assess the ability of the algorithm to deal with intraindividual variability of SNR, a simulation study has been performed. For simplicity, we have considered the reference 3-min sampled simulated CGM profile already used in [16] (see Fig. 2(a), gray dashed line). Then, $N = 100$ CGM time series with time-varying SNR have been created by adding a zero-mean white Gaussian noise profile with time-varying variance σ^2. In order to simulate a time-varying σ^2, a sinusoidal shape has been selected (similar results can be obtained with different choices), with minimum and maximum values equal to 1 and 25 $\mathrm{mg}^2/\mathrm{dL}^2$ (these values are very close to the 10*th* and 90*th* percentiles of the estimates of the noise variance found in [16]). In each of the 100 realizations, the sinusoidal phase has been randomly sampled from a uniform distribution in $(-\pi, +\pi)$, whereas the period is randomly chosen from a uniform distribution in 24–48 h. One representative simulated noisy CGM time series, taken from the set of 100, is reported in Fig. 2(a). The σ^2 profile used to generate the noise for the considered realization is displayed in Fig. 2(d).

B. Qualitative Analysis

Both the new denoising algorithm and the KF presented in [16] have been applied on the dataset. For the representative realization of Fig. 2, the denoised profiles given by the KF and the new method are shown in Fig. 2(b) and (c). Note that, until N samples are collected (dashed vertical line), no filtering can be provided (here, N has been set equal to 120, here 6 h). Both algorithms perform a satisfactory denoising, being the filtered profile close to the reference one. However, the profile obtained with the new method seems more accurate than KF thanks to the continuous real-time estimation of the noise variance $\hat{\sigma}^2$. The time course of the $\hat{\sigma}^2$ estimate obtained with the new method is displayed in Fig. 2(d), together with the true σ^2. The horizontal line denotes the $\hat{\sigma}^2$ value estimated by KF in the *burn-in* and maintained throughout the monitoring. Remarkably, $\hat{\sigma}^2$ profile estimated by the new method is very similar to the true one, demonstrating that the new algorithm is able to correctly track the intraindividual variability of SNR. Note that, since $\hat{\sigma}^2$ is obtained on a sliding window of N samples (i.e., it is an estimation of the "average" σ^2 value of the last 6 h), it is delayed with respect to σ^2. Thus, in order to allow a more fair comparison, the $\hat{\sigma}^2$ profile is compared also with the profile obtained by a moving average of the true σ^2 values in the past 6 h. As one can observe, the superimposition of these two profiles is almost perfect.

In order to better appreciate the improvement given by the new method, let us consider Fig. 3, in which two details of the same representative realization of Fig. 2 are displayed. In both panels, the true glycemia, simulated noisy CGM, denoised CGM with KF and with the new method time series are shown. Panel (a) focuses on the time interval 18–20, where the SNR is high (average $\sigma^2 = 4.3$ $\mathrm{mg}^2/\mathrm{dL}^2$). Here, the smoothing action of the both algorithms is satisfactory and comparable. This is not surprising, because both the new method and the method labeled as KF are tuned with $\hat{\sigma}^2$ values similar to the true one. However, focusing on the time window 9–11 of panel (b), in which the SNR level is significantly lower than in panel (a) (average $\sigma^2 =$ 24.7 $\mathrm{mg}^2/\mathrm{dL}^2$), the amount of smoothness introduced by the

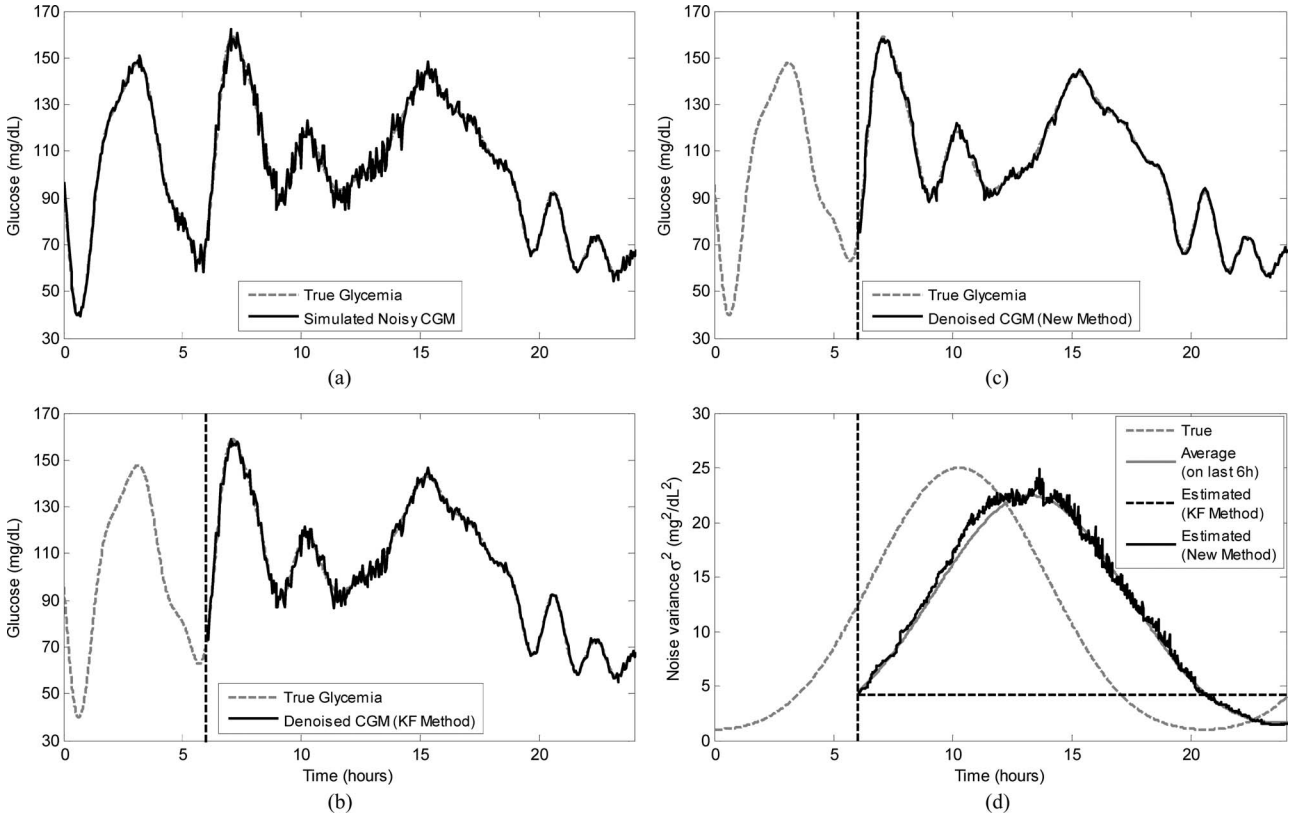

Fig. 2. Simulated study. (a) True glycemia (gray dashed line) and noisy simulated (black line) CGM time series. (b) True glycemia (gray dashed) versus denoised CGM with KF method (black) time series. (c) True glycemia (gray dashed) versus denoised CGM with the new method (black) time series. The dashed vertical line indicates the time when denoising starts. (d) True σ^2 (gray dashed), average σ^2 on last 6 h (gray), estimated σ^2 by KF (black dashed) and by the new method (black).

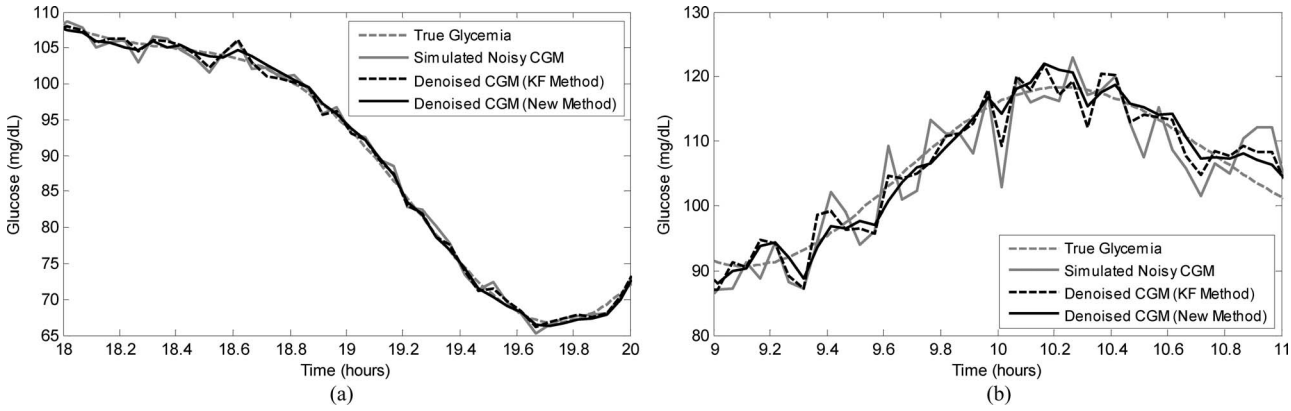

Fig. 3. Simulated study, same representative subject of Fig. 2. Panels (a) and (b) show two zooms on time intervals 18–20 h and 9–11 h, respectively. True glycemia (gray dashed), noisy simulated CGM (gray), denoised CGM with KF (black dashed) and with the new method (black) time series are displayed.

new algorithm results more suited than that suggested by KF. In fact, KF performs undersmoothing because it underestimates the noise variance ($\hat{\sigma}^2 = 4.2$ mg^2/dL^2), reducing only partially the fluctuations due to the noise. On the other hand, the new method performs a much better denoising thanks to the real-time updating of its parameters (in this window, the average $\hat{\sigma}^2$ is 24.9 mg^2/dL^2, very close to true one).

C. Quantitative Analysis

The effect of denoising has also been evaluated quantitatively by resorting to the three indexes already used in [16], i.e., the root-mean-square error (RMSE) (calculated between the denoised and the real profile), the delay introduced by the filter (calculated as the time shift which minimizes the distance between the true and the denoised signal), and the smoothness

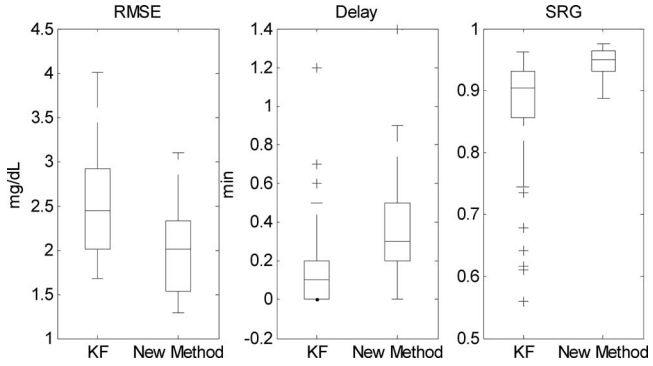

Fig. 4. Boxplots of RMSE, delay, and SRG on the simulated dataset.

relative gain (SRG) (calculated as the normalized difference between the energy of the second order differences of the original and denoised CGM signals, in order to evaluate the regularity increase of the denoised with respect to original CGM profile, see [16] for details).

Focusing on the representative realization of Fig. 3 and comparing the performance of the new method with KF, the RMSE is reduced from 2.4 mg/dL to 1.6 mg/dL, i.e., more than 30%. The delay introduced by the new method and KF are comparable (both 0.2 min), but the SRG of the new method is 0.98, significantly lower than KF (0.88).

Results on all the 100 simulated realizations are summarized in the boxplots of Fig. 4. The RMSE obtained by the new method is significantly lower than that of the method labeled as KF ($p < 0.01$, Wilcoxon RankSum Test), with an average value reduced of about 20% (2.5 and 2.0 mg/dL, respectively). The delay introduced by the new algorithm is slightly higher than KF (less than 0.2 min), but the new method is significantly better than KF in terms of SRG ($p < 0.01$), with the average value increased from 0.88 to 0.95. This demonstrates that the new method performs, on average, significantly better than KF. Focusing on SRG boxplots, it is also worth noting that KF generates many outliers (see plus symbols under the lower whisker). This means that, in some realizations, KF performs suboptimally and it is not able to sufficiently reduce the noise component (the lower the SRG, the lower the improvement in the regularization). On the other hand, the new method does not produce outliers.

IV. Assessment on Real Data

A. Data

The assessment on real data has been performed on the same 24 Glucoday (Menarini Diagnostics, Firenze, Italy) time series (3-min sampling) already considered in [16], to which we refer the reader for details.

B. Qualitative Analysis

Both the new denoising algorithm and the KF presented in [16] have been applied on the dataset. Fig. 5 illustrates the application of KF and the new algorithm to a representative subject, the same already shown in Fig. 1 (similar results have been obtained on all the others). Panel (a) shows original and denoised with KF method CGM signals, and panel (b) displays original and denoised with the new method CGM time series. Both denoised time series are significantly smoother than original CGM. However, the profile obtained with the new method performs a better denoising than KF method. The improvement can be better appreciated by looking at Fig. 6, where two details of Fig. 5 on time intervals 10–13 h and 25–28 h are zoomed on panels (a) and (b), respectively. In each panel, original, denoised with KF method, and denoised with the new method profiles are reported. In panel (a), where the noise variance is lower, KF method performs oversmoothing (visible by eye on the rising front around time 12.5), while in panel (b), where the noise variance is higher, KF method performs undersmoothing (detectable by eye, in particular on the two spikes at time 26 and 27). On the other hand, the new method performs in a satisfactory fashion in both cases thanks to the continuous updating of the variance parameters.

From simulation results, we may also speculate that the estimate of the measurement noise variance profile, shown in panel (c) of Fig. 5, is realistic. Notably, it is far from a constant in time, confirming the need of coping with intraindividual variability of SNR. It ranges from a minimum of 4 mg^2/dL^2 to a maximum of 30 mg^2/dL^2 (about a fivefold factor), with an average $\hat{\sigma}^2 = 14$ mg^2/dL^2 and a percent coefficient of variation of $\hat{\sigma}^2$ equal to 45.9%. The average $\hat{\sigma}^2$ value is an indicator of the mean level of the noise variance in that specific subject, while CV($\hat{\sigma}^2$) is an indicator of the variability of noise variance during the monitoring. For instance, having a CV($\hat{\sigma}^2$) of 50% means that the maximum and minimum values of $\hat{\sigma}^2$differ at least of a factor 3. A second important result is the agreement between the SNR perceivable by eye inspection on a specific time window of the original CGM trace and the correspondent $\hat{\sigma}^2$ returned by the new method. For instance, when the SNR is visibly low (e.g., in the time window 10–13), $\hat{\sigma}^2$ is large (around 13), while when the SNR appears high (e.g., in the time interval 25–28), $\hat{\sigma}^2$ is small (around 28). Similar qualitative results were obtained in all the 24 subjects. Apparent oscillatory components on $\hat{\sigma}^2$, like those which appear in Fig. 5(c), are difficult to analyze because time series is not sufficiently long. It is, therefore, difficult to establish if they are related to specific experimental setup conditions, which can influence signal acquisition or physiology.

C. Quantitative Analysis

Since reporting all the 24 $\hat{\sigma}^2$ profiles is not possible, Table I reports average $\hat{\sigma}^2$ and CV($\hat{\sigma}^2$) values for each subject. As done when analyzing the $\hat{\sigma}^2$ profile of the representative subject, these indexes can help in summarizing characteristics of $\hat{\sigma}^2$ patterns. We can note that the average $\hat{\sigma}^2$ ranges from 1.4 to 32.9 mg^2/dL^2 in subjects #4 and #18, respectively, confirming the presence of an elevated interindividual variability, accordingly to that already emerged in [16]. The CV($\hat{\sigma}^2$) values are likely all close to or greater than 40%, highlighting the presence of an elevated intraindividual SNR variability, as expected, and justifying the necessity of using a denoising procedure able to cope with the intraindividual variability of the SNR.

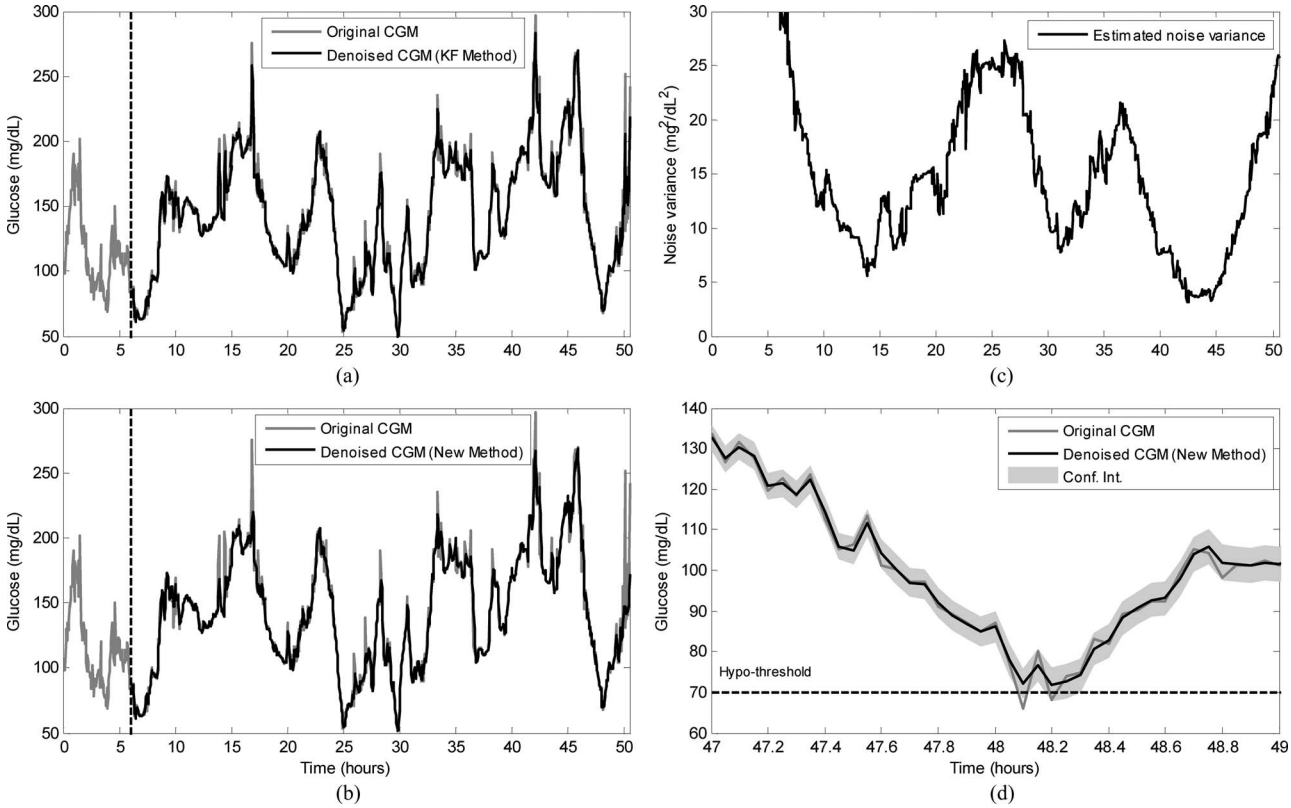

Fig. 5. Real data, subject #14. (a) and (b) CGM originally measured by the Menarini Glucoday system (gray) versus denoised CGM with KF method the new method (black) time series, respectively. The dashed vertical line indicates the time when denoising starts. (c) Estimated σ^2 profile. (d) Zoom of time interval 47–49 h, CGM (gray) and denoised CGM with the new method (black), together with its confidence interval (gray area), time series.

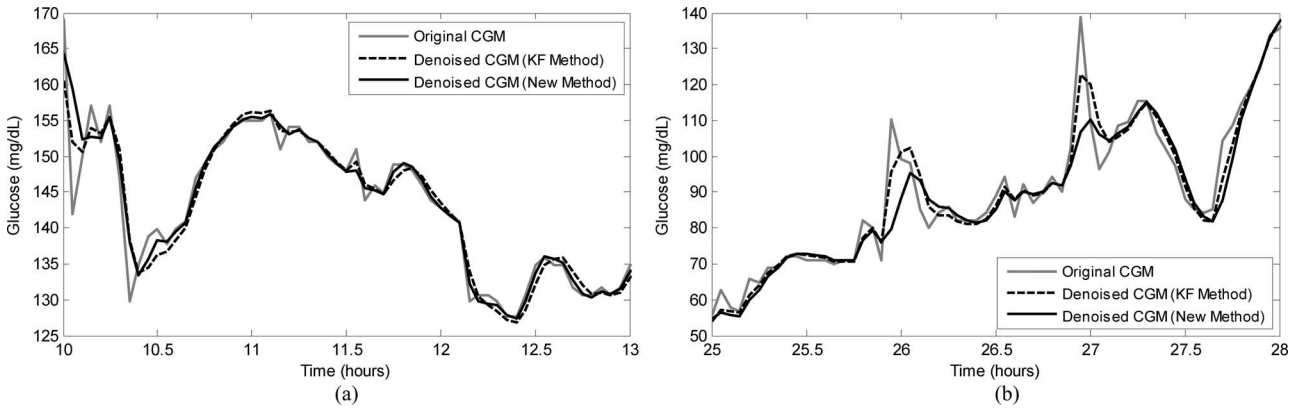

Fig. 6. Real data, subject #14. Details of profiles in Fig. 5(a) and (b) in time intervals 10–13 h (panel (a)) and 25–28 h (panel (b)). CGM (gray), denoised CGM with KF method (black dashed), and denoised CGM with the new method (black) time series.

Finally, to evidence the superiority of the new method to the method of [16], already assessed in simulation of Section III-C, a comparison between them in terms of delay and SRG on all 24 subjects is given in the boxplots of Fig. 7. The delay (left panel) introduced by the new method is not significantly different, on average, from KF ($p = 0.61$). However, concerning SRG (right panel), the smoothing introduced by the new algorithm is significantly greater than KF ($p = 0.05$), with the average value increased from 0.71 to 0.81.

Remark 2: In order to corroborate the assumptions made on whiteness and Gaussianity of measurement noise, we analyzed the residuals in all the 24 subjects. In particular, the mean of the residuals was virtually zero in all subjects, the autocorrelation function did not evidence significant correlations, and the estimated power spectral density was flat, as for a white noise process. Residuals were also compatible with Gaussianity ($p < 0.001$ for all subjects, Lilliefors test).

TABLE I
MEAN AND COEFFICIENT OF VARIATION (CV) OF THE ESTIMATES OF σ^2 FOR EACH SUBJECT OF THE DATASET [16]

	σ^2 estimates	
Subject	Mean (mg^2/dL^2)	CV(%)
1	23.2	40.7
2	6.5	52.5
3	8.3	45.5
4	1.4	72.1
5	13.8	54.2
6	2.7	57.6
7	7.5	68.2
8	2.3	44.9
9	19.9	50.2
10	1.6	111.7
11	9.5	24.0
12	17.8	31.5
13	1.5	148.3
14	14.4	45.9
15	5.7	41.2
16	7.1	62.3
17	10.8	59.6
18	32.9	32.1
19	4.9	48.7
20	15.5	37.4
21	7.2	68.5
22	14.0	65.2
23	8.1	33.3
24	3.7	38.0

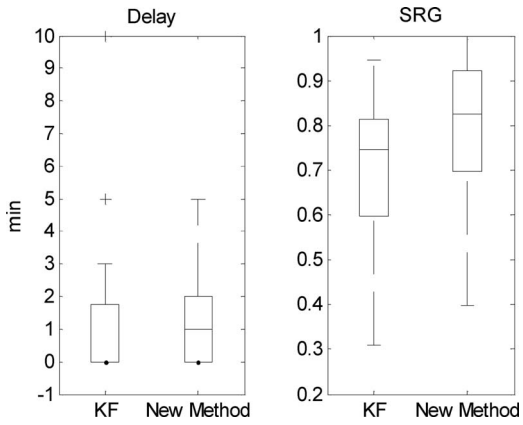

Fig. 7. Boxplots of delay and SRG on the 24 Glucoday time series.

V. CONCLUSION

CGM sensors are key ingredients of several real-time systems aimed at improving diabetes management. However, CGM signals are noisy and it is crucial to improve their quality. Existing online denoising approaches are suboptimal because they employ filters that are not able to take into account that noise variance changes from monitoring to monitoring, and even during the same monitoring. Here, we developed a new denoising method, whose better performance over previous approaches was shown on both Monte Carlo simulation and real CGM data. The method has a general applicability, also outside from the CGM context. In addition, as a by-product, we have also demonstrated that the method can be used to quantify the amount of measurement noise on CGM data.

A possible important added value of the new method in the application of CGM sensors is the possibility of having a statistical description of the denoised glucose readings given by the estimated nominal level and its confidence interval. For instance, Fig. 5(d) shows, for a detail of the profile in Fig. 5(b), the shaded area corresponding to the so-called confidence interval. Notably, the confidence interval varies in time and in agreement with the variance of the measurement noise, i.e., the higher the σ^2, the larger the confidence interval. This information can be useful in an alert generation context. For instance, Fig. 5(d) shows that the risk of generating false hypoglycaemic alerts could be easily handled if the confidence intervals properly used to evaluate the probability that a hypoglycaemic event is occurring.

Finally, in this paper, a white noise structure was used in the covariance matrix of (3). The retrospective analysis of the residuals corroborated this assumption for Menarini Glucoday sensor data. However, the proposed method is flexible with respect to the structure of the noise autocovariance. Obviously, the determination of a more complex shape of the sensor random noise autocovariance would require *ad hoc* experiments to correctly separate physiological from technological noise. For instance, glucose should be frequently measured *in vitro* by a CGM sensor and, simultaneously, also by a gold standard technique. This would rule out interferences such as those given in vivo by plasma-to-interstitial fluid kinetics. To the best of our knowledge, similar data have never been published.

ACKNOWLEDGMENT

Data are courtesy of Dr. A. Maran, Department of Cinical and Experimental Medicine, University of Padova, Padova, Italy.

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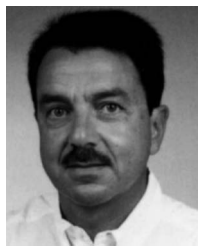

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