An Online Self-Tunable Method to Denoise CGM Sensor Data

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

***Abstract*—Continuous glucose monitoring (CGM) devices can be very useful in diabetes management. Unfortunately, their use in online applications, e.g., for hypo/hyperalert generation, is made difficult by random noise measurement. Remarkably, the SNR of CGM data varies with the sensor and with the individual. As a consequence, approaches in which filter parameters are not allowed to adapt to the current SNR are likely to be suboptimal. In this paper, we present a new online methodology to reduce noise in CGM signals by a Kalman filter (KF), whose unknown parameters are adjusted in a given individual by a stochastically based smoothing criterion exploiting data of a burn-in interval. The performance of the new KF approach is quantitatively assessed on Monte Carlo simulations and 24 real CGM datasets. Our results are compared with those obtained by a moving-average (MA) filtering approach with fixed parameters currently in use in likely all commercial CGM devices. Results show that the new KF approach performs much better than MA. For instance, on real data, for comparable signal denoising, the delay introduced by KF is about 35% less than that obtained by MA.**

***Index Terms*—Alert, biomedical signal processing, diabetes, Kalman filter (KF), signal denoising.**

I. Introduction

GLUCOSE is the most important fuel for human beings and its level in the blood is tightly controlled by insulin by a negative feedback system. Diabetes is a chronic disease that affects about 250 million people in the world. In diabetic patients, the body does not secrete insulin (Type 1 diabetes) or derangements in both insulin secretion and action (Type 2 diabetes) occur. Diabetes therapy is mainly based on insulin, diet, drug administration, and physical exercise, tuned according to self-monitoring of blood glucose (SMBG) measurements collected three to four times a day [1]. SMBG analysis is extremely useful to evaluate the adequacy of the therapeutic protocol and also to highlight, e.g., long-term trends and instability [2]. However, the metabolic control based on SMBG is usually suboptimal, and glucose concentration often exceeds the normal range thresholds (70–180 mg/dL). Hyperglycemia is mostly responsible for long-term complications, such as neuropathy, retinopathy, and cardiovascular and heart diseases, while hypoglycemia is risky in the short-term, since even mild or moderate hypoglycemia can rapidly turn into dangerous episodes, possibly also leading to hypoglycemic coma.

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A. Facchinetti and G. Sparacino are with the Department of Information Engineering, University of Padova, Padova 35131, Italy (e-mail: facchine@dei.unipd.it; gianni@dei.unipd.it).

*C. Cobelli is with the Department of Information Engineering, University of Padova, Padova 35131, Italy (e-mail: cobelli@dei.unipd.it).

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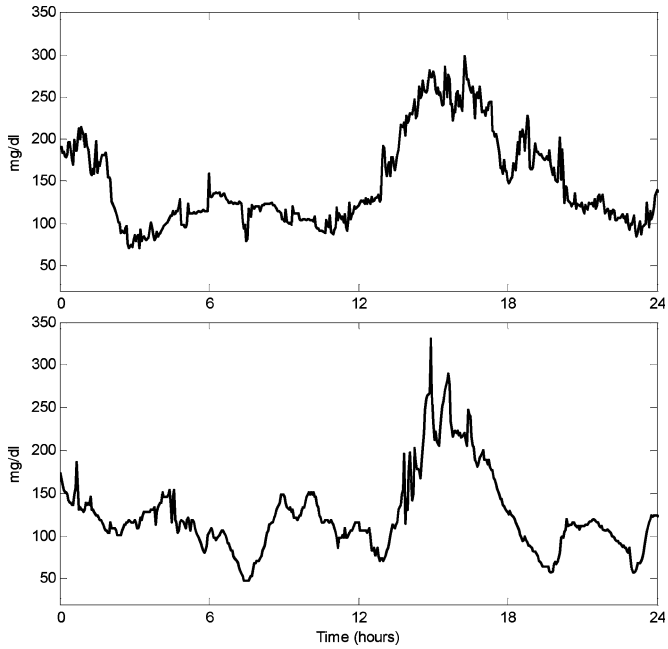

Fig. 1. Two representative CGM time-series measured for 24 h, at 3-min sampling rate, in two diabetic subjects by Glucoday. (Top) Low-SNR condition. (Bottom) High-SNR condition.

In the past few years, the achievement of a more accurate control seems possible due to the development of continuous glucose monitoring (CGM) devices [3]–[5]. These devices allow to measure glucose concentration for several days, e.g., 7 to 14 days, in a quasi-time-continuous manner, e.g., every minute. Retrospective data analysis of CG readings can be very useful in tuning/refining diabetes therapy [6]. In a real-time perspective, a natural application of CGM devices concerns with the early detection of hypo/hyperglycemic episodes. For instance, by comparing the currently measured (or predicted ahead of time) glucose level with a given hypo/hyperthreshold, an alert could be generated [7]–[10]. An efficient generation of hypo/hyperalerts can be of dramatic importance in the short-term, e.g., a dangerous nocturnal hypoglycemia. Unfortunately, the performance of alert systems implemented in commercial devices, such as [11], [12] is still rather poor, with a percentage of false alerts of the order of 50% [10].

The probability of either generating false positive alerts or missing true events obviously depends on the quality of CGM data. Unfortunately, CGM data are noisy. This is evident from Fig. 1, which illustrates two representative time-series (black line) measured in two diabetic subjects through a commercial CGM device, the Glucoday (Menarini, Firenze, Italy), a minimally invasive microdialysis sensor that provides glucose

readings for every 3 min (data taken from [13], where details on the sensor can be found). In the top panel, 1-day CGM data of subject #10 are clearly corrupted by a large noise component. On the other hand, the bottom panel shows 1-day CGM data of subject #8, in which the noise variance appears, in general, smaller than for subject #10, even if large spurious spikes (possibly due to patient movements, which episodically may perturb sensor behavior) are present.

It must be noted that several sources of error can affect the accuracy of CGM data. In particular, an error component is often present due to imperfect calibration [14], [15]. Another source of error (which sometimes is lumped together with the random noise component, see later) is related to the sensor physics, chemistry, and electronics [16]. Finally, the CGM signal is also corrupted by a random noise component [17], which dominates the true signal at high frequency. In this paper, we will deal with the reduction of this last component.

Digital filtering techniques can be used in order to enhance the quality of the signal and reduce the random noise component of the error. In more formal terms, if we consider the following equation:

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

where $y(t)$ is the glucose level measured at time t, $u(t)$ is the true, unknown, glucose level, and $v(t)$ is the random noise affecting it, which is supposed to be additive. The purpose of filtering is to recover $u(t)$ from $y(t)$. Given the expected spectral characteristics of noise, i.e., noise is white, (causal) low-pass filtering represents the most natural candidate to separate signal from noise in online applications [18]. One major problem in low-pass filtering is that, since signal and noise spectra normally overlap, it is not possible to remove the random noise $v(t)$ from the measured signal $y(t)$ without distorting the true signal $u(t)$. In particular, distortion results in a delay affecting the estimated $\hat{u}(t)$ with respect to the true $u(t)$; the more the filtering, the larger the delay. It is easily understood that having a consistently delayed, even if less noisy, version of CGM data could be useless in practice, e.g., for the generation of timely hypoalerts. A clinically significant filtering issue is thus the establishment of a compromise between the regularity of $\hat{u}(t)$ and its delay with respect to the true $u(t)$.

The purpose of this paper is to present and assess a new approach, developed within a Bayesian estimation embedding [18] and implemented by Kalman filtering (KF), for the online denoising of CGM signals. A key feature of the method is that, due to the incorporation of a stochastically based smoothing criterion, it can individualize filter parameters, and hence, the regularization amount, according to the SNR of the specific CGM signal. The performance of the new KF approach is quantitatively assessed on Monte Carlo simulations and 24 real CGM datasets, and compared to a moving-average (MA) filtering approach with fixed parameters currently in use in likely all commercial CGM devices. Results show that the new KF approach performs much better than MA. For instance, on real data, for comparable signal denoising, the delay introduced by KF is about 35% less than that obtained by MA.

II. Online Denoising of CGM Data: State of the Art

In the literature, online denoising of CGM signals has been addressed, both by sensor manufacturers and scientists, only indirectly. In fact, much more emphasis has been given to the prediction of future glucose levels using CGM sensors [8], [9], [15], [17], and [19]. However, online filtering in order to enhance the SNR can be beneficial in many applications, including the improvement of glucose predictors [20] and closed-loop control strategies [21]–[23]. To the best of our knowledge, in the CGM literature, no work has directly addressed the challenges posed by the denoising of CGM data, e.g., the variability of the SNR. Next, we briefly illustrate the state of the art and evidence some open issues.

A. Denoising Filters in Commercial CGM Devices

Understanding how signals are elaborated inside commercial CGM devices is often difficult. For example, in both the patents of Feldman and McGarraugh [24], relative to the FreeStyle Navigator (Abbott Diabetes Care, Alameda, CA), and Simpson *et al.* [25], relative to the Seven (DexCom, Inc., San Diego, CA), digital filtering for the output enhancement is mentioned, but no details are reported. Information on how denoising is performed in the CGMS (Medtronic Minimed, Inc., Northridge, CA) can be found in the patent of Mastrototaro *et al.* [26], where basically a MA filter is used. Therefore, MA can be considered the state of the art in CGM technology.

MA is a linear causal approach that is commonly used in denoising in many applications. Briefly, having fixed the order k, the output of the filter relative to the nth sample is given by a weighted sum of the last k-measured samples

$$\hat{u}(n) = \frac{w_1 y(n) + w_2 y(n-1) + \cdots + w_k y(n-k+1)}{\sum_{i=1}^{k} w_i} \tag{2}$$

where $y(n)$ represents glucose of the nth sample. The parameters of the filter are the order k and the weights $w_1, \ldots, w_k$. The higher k is, the longer is the "memory" of the past data. Increasing k usually produces a more significant noise reduction and, at the same time, a larger signal distortion, e.g., $\hat{u}(n)$ is significantly delayed, thus being unable to track fast changes of the true $u(n)$. Having fixed the order k, the weights $w_1, \ldots, w_k$ can be chosen in several ways. The most common strategy is an MA with exponential weights, where $w^i = \mu^i$, with μ (a real between 0 and 1) acting as a "forgetting factor" (the higher μ, the higher the memory of past data). The major weakness of MA is that, once weights have been chosen, it treats all the time series in the same way, irrespectively of possible differences of their SNR due to sensor and individual variability (see Fig. 1). As a consequence, a filter with fixed parameters is likely to be suboptimal in denoising CGM data.

B. Literature State of the Art

Chase *et al.* [17] proposed an integral-based fitting and filtering method to reduce the effect of measurement errors. Even if the procedure can be used in real time during clinical trials, its major limitation consists of the fact that some of its components

(e.g., the concentration of plasma insulin) cannot be identified if only CGM data are available. This hinders the possibility of using the method in daily-life conditions.

The first use of the KF to process CGM data was presented in the work of Knobbe and Buckingham [19]. However, the aim of this paper was to reconstruct blood glucose concentration, and not to denoise CGM data. To do this, a model of blood-to-interstitium glucose kinetics and blood glucose references are needed.

Optimal estimation by using KF has also been proposed by Palerm *et al.* [8], [9], with the aim of predicting the glucose profile and detecting hypoglycemia, and by Kuure-Kinsey *et al.* [15], with the purpose of improving CGM calibration.

1) Brief Overview of KF: Briefly, at discrete time, the KF is implemented by first-order difference equations that recursively estimate the unknown state vector $x(t)$ of a dynamic system exploiting vectors of noisy measurements $y(t)$ causally related to it [18], [27]. The process update equation is given by

$$x(t+1) = Fx(t) + w(t) \tag{3}$$

where $x(t)$ has, in general, size n, $w(t)$ is usually a zero-mean Gaussian noise vector (size n) with (unknown) covariance matrix Q (size $n \times n$), and F is a suitable matrix (size $n \times n$). The state vector $x(t)$ is linked to the measurement vector $y(t)$ (size m) by the equation

$$y(t) = Hx(t) + v(t) \tag{4}$$

where $v(t)$ is the zero-mean Gaussian noise measurement error vector (size m) with (unknown) covariance matrix R, and which is uncorrelated with $w(t)$, and H is a suitable matrix (size $m \times n$). The linear minimum variance estimate of the state vector obtainable from the measurements $y(t)$ collected till time t is indicated by $\hat{x}(t|t)$, and can be computed by using the following linear equations:

$$\begin{cases} K_t = (FP_{t-1|t-1}F^T + Q)H^T(H(FP_{t-1|t-1}F^T + Q)H^T + R)^{-1} \\ \hat{x}(t|t) = F\hat{x}(t-1|t-1) + K_t(y(t) - H\hat{x}(t-1|t-1)) \\ P_{t|t} = (1 - K_tH)(FP_{t-1|t-1}F^T + Q) \end{cases} \tag{5}$$

where $P_{t|t}$ (size $n \times n$) is the covariance matrix of the estimation error affecting $\hat{x}(t|t)$, K_t (size $n \times m$) is the Kalman gain matrix, and $P_{0|0}$ and $\hat{x}(0|0)$ are the initial conditions. The Q and R matrices, i.e., the process and the measurement noise covariance matrices (respectively), are key parameters in determining the performance of KF. Unfortunately, Q and R are usually unknown, or sometimes, they are known except for a scale factor. The major problem of KF is the determination of Q and R, and, more specifically, of the so-called Q/R ratio [18], [27]. This problem bears a close resemblance to determining the smoothing parameter in regularization methods [28]–[30].

2) Application to CGM Time-series: In all the approaches discussed above applying KF to CGM signals [8], [9], and [15], major limitations are: the Q/R ratio is tuned off-line and retrospectively all over the data, thus making this kind of approach not usable in real-time applications; the Q/R ratio is not individualized in order to cope with the variability of the SNR from subject to subject. As it appears from the two panels of Fig. 1, the SNR can be significantly different from individual to individual, so that individualization of Q/R is essential to avoid suboptimality of KF, as it will be quantitatively demonstrated in Section IV.

C. Aim of the Paper

The aim of this paper is to illustrate a new approach developed within a Bayesian estimation embedding [18] for the online denoising of CGM signals. The methodology uses a KF implementation, which, at variance of that already published [8], [9], [15], exploits the key feature of incorporating a stochastically based smoothing criterion for the determination of the unknown Q/R ratio. As a result, the method can work in real time, is self-tunable, and is able to cope both with SNR variations from individual to individual and from sensor to sensor. The performance of the new KF approach will be quantitatively assessed on Monte Carlo simulation and 24 real CGM datasets.

III. Online Self-Tunable Approach

A. A Priori Model for $u(t)$

Calling back the notation used in (1), if some *a priori* information on $u(t)$ is available, an "optimal" filter (i.e., determining the best tradeoff between noise reduction and signal distortion) can be determined by embedding the filtering problem within a Bayesian context, where the KF can be adopted in the implementation step [18].

An *a priori* description of the unknown signal is, however, necessary. A simple but flexible way to model a smooth signal on a uniformly spaced discrete grid is to describe it as the realization of the multiple integration of a white noise process. The choice of the number of integrators, to the best of our knowledge, cannot be easily addressed on firm theoretical basis. As a matter of fact, in the smoothing/regularization literature, the choice of m is normally left to the user or handled on empirical bases [31]. In our case, $u(t)$ can be reliably described as the double integration (the so-called integrated random-walk model) [30], we have

$$u(t) = 2u(t-1) - u(t-2) + w(t) \tag{6}$$

where $w(t)$ is a zero-mean Gaussian noise with (unknown) variance equal to λ^2. The choice of $m = 2$ integrators emerges from a simulation study using a cross-validation strategy similar to that of [29], [32], and [33] (for sake of space not documented here). Bringing (6) into the state space, two state variables, i.e., $x_1(t) = u(t)$ and $x_2(t) = u(t-1)$, are needed. Then, in (3) the state-space vector at time t becomes $x(t) = [x_1(t)x_2(t)]^T$, and F is consequently given by

$$F = \begin{bmatrix} 2 & -1 \\ 1 & 0 \end{bmatrix}. \tag{7}$$

Reminding that the CGM measurement is the only output of the system, the measurement vector $y(t)$ of (4) becomes scalar, and $H = [1 \quad 0]$. Updating (5) for the estimation of $\hat{x}(t|t), P_{t|t}$ becomes a 2×2 matrix (with $P_{0|0} = I_2$ and $=$

$[y(0)y(-1)]^T)$, K_t a 2×1 vector, and Q and R are

$$Q = \begin{bmatrix} \lambda^2 & 0 \\ 0 & 0 \end{bmatrix} \qquad R = \sigma^2. \tag{8}$$

In order to arrive at an estimate of glucose $\hat{u}(t)$, both λ^2 and σ^2 are required. In our problem, neither λ^2 nor σ^2 are known, and we need to estimate their values in real time from the data. An additional difficulty is that, as noted at the end of Section I, the SNR can vary from sensor to sensor and from individual to individual. This variability suggests that "universal" λ^2 and σ^2 estimates cannot be used for all individuals, but their values need to be individualized, calling for a real-time and self-tunable parameter-estimation procedure in order to make KF really online applicable.

B. Determination of λ^2 and σ^2

As seen in Section II-B, the λ^2 and σ^2 estimation problems (i.e., the Q/R ratio estimation) have already been faced in the literature [8], [9]. However, in these studies, parameters are retrospectively tuned and are not individualized. In order to solve both these problems, we propose the following two-step procedure for the estimation of λ^2 and σ^2.

Step 1: The first portion (here a 6-h window) of each time series is considered as a tuning interval, where the unknown parameters λ^2 and σ^2 are automatically estimated using a stochastically based smoothing criterion based on maximum likelihood (ML). Briefly, approaching the problem of smoothing the data of the tuning interval in vector y (in this case y contains all the measurement collected in the 6-h period) as a linear minimum-variance estimation problem, one has to solve

$$\hat{u} = \arg\min_{u} \left\{ (y-u)^T (y-u) + \left(\frac{\sigma^2}{\lambda^2}\right) u^T L^T L u \right\} \tag{9}$$

where the first term of the cost function on the right-hand side measures the fidelity to the data, while the second term weights the roughness of the estimate, L being square of lower triangular Toeplitz matrix whose first column is $[1,-2,1,0,\ldots,0]^T$. When both σ^2 and λ^2 are unknown, the minimization problem of (9) should be solved for several trial values of the regularization parameter $\gamma = \sigma^2/\lambda^2$ until

$$\frac{\text{WRSS}(\gamma)}{n-q(\gamma)} = \gamma \frac{\text{WESS}(\gamma)}{q(\gamma)} \tag{10}$$

where $\text{WRSS} = (y-\hat{u})^T(y-\hat{u})$, $\text{WESS} = \hat{u}^T L^T L \hat{u}$, $q(\gamma) = \text{trace}(I_k + \gamma L^T L)^{-1}$, I_k is k-size identity matrix, and k being the number of measured CGM samples in the selected window (here 6 h). As γ is determined, the estimate of σ_2 is given by

$$\hat{\sigma}^2 = \frac{\text{WRSS}(\gamma)}{n-q(\gamma)}. \tag{11}$$

The regularization criterion of (10) has interesting connections both with some average properties of linear minimum-variance estimators [34] and data-likelihood maximization [30] (for more details, we address the reader to the quoted papers).

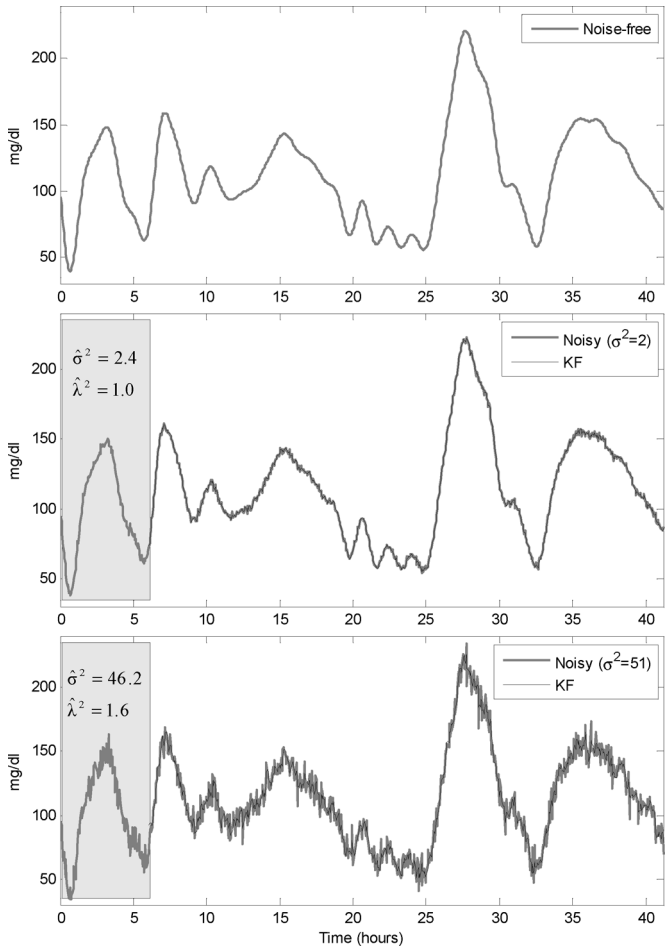

Fig. 2. Simulated study. (Top) Noise-free CGM data (3-min sampling rate). (Middle) Representative high-SNR ($\gamma^2 = 2$), noisy (gray line) versus KF (thin black line) time-series. (Bottom) Representative low-SNR ($\gamma^2 = 51$), noisy (gray line) versus KF (thin black line) time-series. The gray box is the 6-h tuning interval (estimated parameters are reported inside).

Step 2: For the rest of the data, the values of λ^2 and σ^2 found at Step 1 are used in (5) and (8), allowing both real-time application of KF and individualization of KF parameters.

IV. Assessment on Simulated Data

In order to demonstrate the necessity of individualization of filter parameters and the reliability of the new methodology, a Monte Carlo simulation study has been performed.

A. Accuracy in Determination of Actual SNR

A reference noise-free 3-min sampled glucose profile (see Fig. 2, top panel, thick gray line) was first created. Then, $N = 300$ noisy time-series have been generated by adding to the reference profile a zero-mean white Gaussian noise sequence [17] with variance σ^2 randomly sampled in the interval (1100) mg^2/dL^2. Two representative profiles with high and low SNR (obtained for realizations of σ^2 equal to 2 and 51, respectively) are shown in middle and bottom panels of Fig. 2 (thick gray lines), respectively. In both panels, σ^2 and λ^2 estimates, obtained by applying the procedure described in Section III-B,

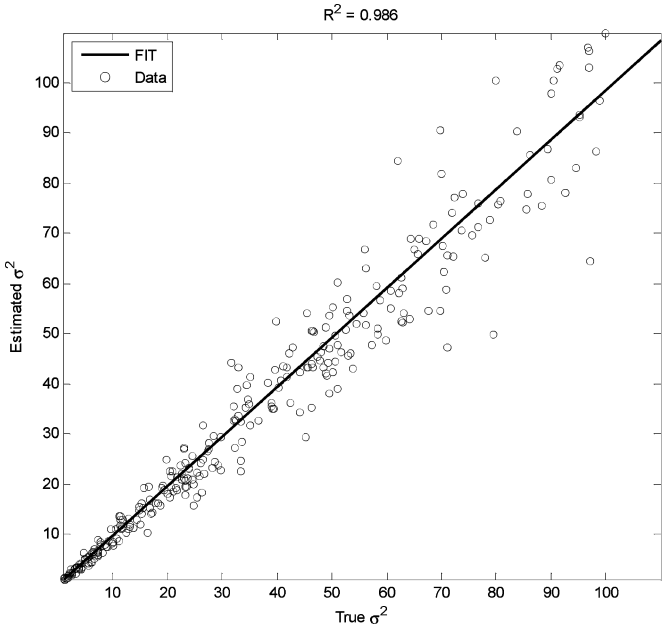

Fig. 3. True versus estimated γ^2 values (black circles). The black solid line is the fit of the data ($R^2 = 0.986$).

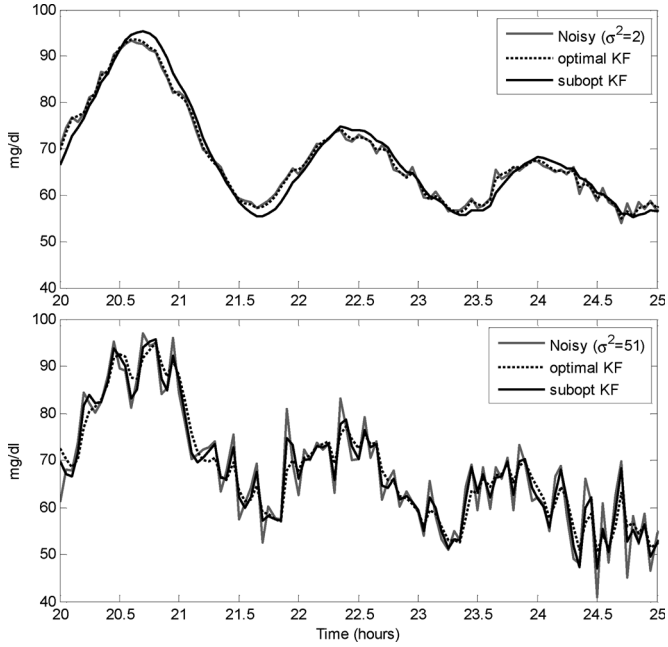

Fig. 4. Suboptimal filtering. Noisy (gray line), optimal KF-filtered (black dashed line), and suboptimal KF-filtered (black line) time-series. (Top) Oversmoothing case, real $\gamma^2 = 2$, used $\gamma^2 = 46.2$. (Bottom) Undersmoothing case, real $\gamma^2 = 51$, used $\gamma^2 = 2.4$.

are reported inside the gray box, which represents the 6-h tuning interval. Estimated σ^2 values are 2.4 and 46.2, very similar to true values. The KF output (tuned with parameters estimated in the 6-h window) is displayed by thin black line. In these two realizations, the RMSE is equal to 1.2 and 4.5 mg/dL, respectively.

Results of the application of the criterion of (10) for all $N = 300$ simulations show that the measurement noise variance σ^2 is estimated very well. Fig. 3 displays the comparison between true and estimated σ^2 values in $N = 300$ runs, with a correlation coefficient $R^2 = 0.986$. Looking at the so-called Q/R ratio, estimated γ values are very different, with an average value of 21.6, and 10th and 90th percentile of 3.3 and 48.2, respectively. In addition, the estimation of the process noise variance λ^2 for all the $N = 300$ realizations returned an average value of 1.5, with 10th and 90th percentile of 1.0 and 2.1 mg^2/dL^2, respectively (meaning that the variability of λ^2 is correctly estimated, irrespective of the SNR).

B. Importance of Filter Parameters Accuracy

Here, we demonstrate the necessity of filter parameters individualization. The top panel of Fig. 4 displays a zoom of what happens if the signal of Fig. 3 (middle panel) is filtered using parameters obtained for the signal of Fig. 3 (bottom panel). As apparent, the use of suboptimal parameters in this case leads to oversmoothing, introducing possibly critical under/overshoots when signal derivative changes, and large temporal delay (e.g., 6 min around 20.7 h). Conversely, if the signal of Fig. 3 (bottom panel) is filtered with the parameters obtained for the signal of Fig. 3 (middle panel), an undersmoothing situation is generated, with a RMSE increase of about 27% (5.7 versus 4.5 mg/dL).

TABLE I
AVERAGE VALUES OF T AND RMSE, TOGETHER WITH 10TH AND 90TH PERCENTILES COMPUTED FOR MA AND NEW KF ON ALL $N = 300$ REALIZATIONS

	T (min)		RMSE (mg/dl)	
	MA	KF	MA	KF
Average	3.5	0.4	3.6	3.5
10th perc	3.0	0.1	2.3	1.5
90th perc	4.0	1.0	5.0	5.4

C. Comparison With MA

In order to further illustrate the novelty of the new KF methodology, its outcome in the $N = 300$ simulations was compared with that of a MA filter with exponential fixed weights determined (after a preliminary study, here not documented for sake of space) by setting k and μ equal to 5 and to 0.65, respectively. The filter performance is quantitatively assessed by considering both the RMSE and the delay with respect to the original noise-free signal. Such a delay is measured by the index T, defined as the temporal shift (in minutes) that has to be applied to $\hat{u}$ in order to minimize the squared norm of the difference between $\hat{u}$ and y, i.e.,

$$T = \arg\min_{T} \sum_{i} (y(t) - \hat{u}(i+T))^2. \tag{12}$$

Table I shows the average values of RMSE and T together with their 10th and 90th percentile. Even if the RMSE are not significantly different (Wilcoxon rank-sum test, $p = 0.39$), the delay T is significantly lower (Wilcoxon rank-sum test, $p < 0.001$), with an average value that has been reduced by about 90% (0.4 versus 3.5 min). In addition, the delay introduced by

KF is, in the worst case, lower than the delay of MA in the best case (2.2 versus 2.3 min, not documented here for sake of space). In summary, the performance of the new KF is quantitatively much better than a filter with fixed parameters, giving a similar estimation of the noise-free profile with a minimum delay.

V. Assessment on Real Data

The database used for the test consists of 24 time-series, taken from a larger study [13], collected in Type 1 diabetic patients using the Glucoday system (Menarini Diagnostics, Firenze, Italy). Both MA and the new KF have been applied.

Before filtering, the time series were preprocessed through a simple causal nonlinear procedure aimed at reducing the amplitudes of occasional nonphysiological spikes. In particular, each glucose sample is compared with the previous one, and, if the absolute difference (relative to the sampling period) is higher than the physiological limit of 4 mg/dL per minute [35], it is corrected accordingly. This hard-bounding procedure is similar to that employed within the Minimed CGMS device [36].

The performance of the two filtering approaches has been assessed by considering both the delay measured by index T of (12) and the regularity of the filtered signal (note that the RMSE as done previously in the simulation context) measured by the smoothness relative gain (SRG) index defined as

$$\text{SRG} = \frac{\text{ESOD}(y) - \text{ESOD}(\hat{u})}{\text{ESOD}(y)} \tag{13}$$

where ESOD(u) denotes the energy of the second-order differences of a time series u, a regularity index already proposed in a CGM prediction context in [20]. SRG is an index, which varies between 0 and 1, and measures the relative amount of signal regularity introduced by (low-pass) filtering.

Fig. 5 shows the results of application of both MA (black dotted line) and the new methodology (black solid line) on the same two representative real subjects illustrated in Fig. 1. In order to better highlight the most important features coming out from the comparison, two 6-h windows have been selected. For subject #10 (top panel), $\hat{\sigma}^2$ results equal to 17.1 mg^2/dL^2, quantitatively confirming the presence of a rather low SNR, which could be also detected by eye inspection. KF produces a very good denoising, with $T = 4.6$ min lower than MA (where $T = 7.0$ min), and SRG $= 0.91$ higher than MA (where SRG $=$ 0.90), meaning that it is able to perform a similar smoothing introducing less delay. For subject #8 (bottom panel), where the SNR appears lower than in subject #10 also by eye inspection, a lower value for the measurement noise variance is estimated ($\hat{\sigma}^2 = 3.5$ mg^2/dL^2). From a quantitatively point of view, KF gives a profile with SRG $= 0.86$ and $T = 1.4$ min, while with MA returns SRG $= 0.91$ and $T = 3.5$ min. Results highlight the fact that, in subject #8, MA clearly produces oversmoothing, while KF, thanks to the individualization of the parameters, correctly detect a high SNR. Table II reports T and SRG values for each of the 24 subjects of the dataset, together with their mean and 10th and 90th percentiles. On average, we can observe that the SRG has been reduced only by 0.03, while the delay T introduced by KF is significantly smaller (-35%) than MA

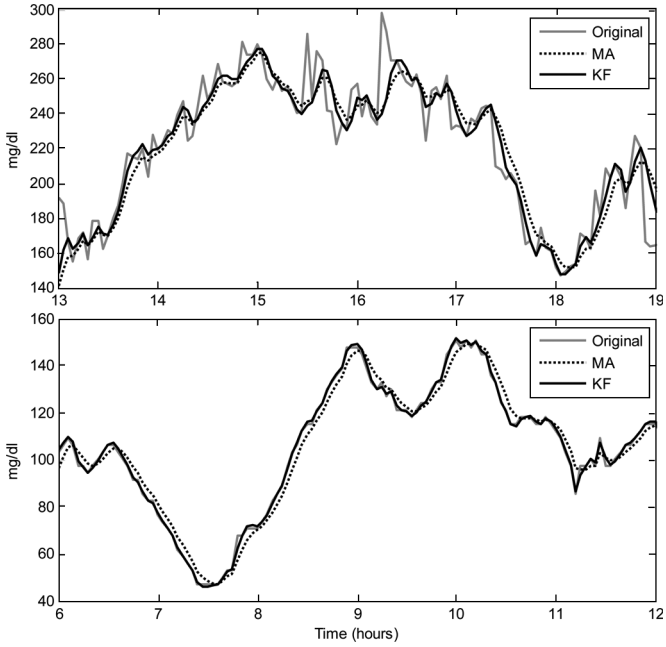

Fig. 5. Two representative 6-h windows of real data. Original (gray line), MA-filtered (black dashed line), and KF-filtered (black line) time-series. (Top) Subject #10, low-SNR condition. (Bottom) Subject #8, high-SNR condition.

TABLE II
T and SRG for Both MA and New KF in Each of 24 Subjects, Together With Average, 10th and 90th Percentiles Values

	T (min)		SRG			
Subject	**MA**	**KF**	**MA**	**KF**	**σ^2**	**γ**
1	5.5	1.6	0.91	0.94	12.3	0.4
2	3.5	1.4	0.89	0.84	5.1	0.2
3	6.0	3.0	0.88	0.86	3.7	1.3
4	3.5	0.4	0.88	0.73	1.1	2.4
5	5.0	8.2	0.90	0.93	4.0	9.6
6	4.0	0.6	0.88	0.81	3.8	11.5
7	6.0	3.4	0.87	0.78	20.7	1.9
8	3.5	0.2	0.91	0.86	3.5	0.5
9	3.5	1.4	0.89	0.83	2.1	1.7
10	7.0	4.6	0.90	0.91	17.1	0.0
11	5.5	2.6	0.89	0.83	5.1	2.0
12	5.5	2.8	0.89	0.89	13.3	0.4
13	4.5	1.2	0.86	0.74	9.7	2.2
14	5.0	8.0	0.90	0.86	31.7	0.2
15	3.5	1.0	0.90	0.86	7.8	0.2
16	5.0	1.2	0.90	0.89	11.8	1.1
17	4.5	2.8	0.90	0.86	3.7	2.0
18	5.0	5.2	0.91	0.94	20.7	0.2
19	5.5	2.4	0.89	0.73	9.6	1.7
20	4.5	5.8	0.89	0.89	25.1	0.6
21	4.0	2.6	0.90	0.89	10.6	0.1
22	6.0	6.4	0.90	0.86	8.0	4.2
23	5.5	2.8	0.89	0.84	8.4	0.2
24	11.5	9.8	0.89	0.95	7.8	2.5
Average	**5.1**	**3.3**	**0.89**	**0.86**	**10.3**	**2.0**
10th perc	3.5	0.7	0.88	0.75	3.5	0.2
90th perc	6.0	7.5	0.91	0.94	20.7	3.7

The last two columns show σ^2 and γ estimated in the burn-in interval.

($p < 0.01$, Wilcoxon rank-sum test). Interestingly, the 10th and 90th percentiles of both T and SRG correspond to rather wide intervals, suggesting that KF, with parameters tuned according to the statistically based criterion and according to the individual SNR, is able to tune the proper smoothing in different SNR conditions, and therefore, it is an effective solution to problem of the SNR variability from individual to individual.

A few comments are in order on the last two columns of Table II. In the first column, σ^2 estimated values are reported for each subject. As it clearly appears from the 10th and 90th percentile values (3.5 and 20.7 mg^2/dL^2), the measurement noise variance is very different from an individual to another, numerically resembling what has been observed by graphical inspection. Furthermore, in the second column, γ estimated values are reported. The regularization parameter γ, which we remind to be the so-called Q/R ratio, and which is estimated in the 6-h tuning interval, results very different between individuals. The fact is not surprising, resembling the observation on the need of filter parameters individualization made in Section IV, in which more than one order of growth rate was detected. Quantitatively, on the real dataset, the difference between the maximum (11.45) to minimum (0.04) values is about of three orders of growth rate. This confirms also on real data the necessity of parameters individualization to avoid suboptimal filtering.

VI. Conclusion

CGM systems can be very useful in the management of diabetes, e.g., for the detection of hypo/hyperglycemic events. Unfortunately, CGM data are affected by several sources of error, including bias errors (due to imperfect/loss of calibration or to the physics/chemistry of the sensor) and random noise, which dominates the true signal at high frequency. In this paper, we have dealt with the reduction of this last component by online digital filtering. Available online denoising approaches, either already present in commercial CGM devices or simply proposed in the scientific literature, have significant practical limitations, i.e., it is impossible to determine in real-time filter parameters and to adapt them to the individual SNR. In this paper, we have proposed a new online self-tunable CGM filtering methodology implemented by KF. Rather than in the application of KF to CGM signals per se, the novelty of the method is the possibility of using a stochastically based smoothing criterion, which can work in real time to cope both with SNR variations from individual to individual and from sensor to sensor. It is important to note that the proposed procedure is applicable to denoise the signal (in the sense above) even when other "low-frequency" components of error (e.g., calibration errors) are present. In this case, the filtered signal will be improved because of the reduction in spurious oscillations due to random noise, but it will be still affected by a bias error.

The performance of the new KF technique has been assessed first by a Monte Carlo simulation study with $N = 300$ realizations. Results show that online tuning and individualization on KF parameters are necessary to avoid suboptimal filtering, and that the method reliably determines the variance σ^2, and hence, effectively deals with different SNR. The analysis of 24 real CGM time-series-supported simulation results demonstrate that the new KF performs much better than the MA method used in commercial devices.

From a clinical point of view, the reduction of the time lag introduced by the filter can be of remarkable importance, because it can allow the CGM device to generate hypo/hyperglycemic alerts more timely, thus reducing the time spent in hypo/hyperglycemia by the patient. In addition, the improvement of the quality of the CGM signal can limit the number of false alerts, which is of crucial importance, especially overnight.

In conclusion, due to the online and fully-automated tuning procedure for KF parameters estimation, the proposed KF approach is able to cope with both sensor-to-sensor and individual-to-individual SNR variability of CGM data, and due to the all the real-time features, it can be embedded in CGM devices to improve their performance, e.g., to avoid false alerts in the generation in hypo/hyperalarms. Further development of this approach will consist in extending the method in order to cope with the possible variability of the SNR during the same monitoring.

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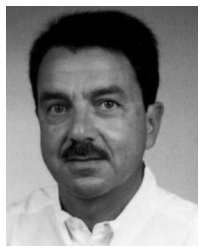
Andrea Facchinetti was born in Padova, Italy, on July 27, 1981. He received the Doctoral degree (Laurea) (*cum laude*) in information engineering and the Ph.D. degree in bioengineering from the University of Padova, Padova, Italy, in 2005 and 2009, respectively.

He is currently a Postdoctoral Researcher with the University of Padova. His research interests include modeling, analysis, and prediction of glucose time-series, and the development of gene ontology-based algorithms for the prediction of functions of anonymous proteins.

Giovanni Sparacino was born in Pordenone, Italy, on November 11, 1967. He received the Doctoral degree (*cum laude*) in electronics engineering from the University of Padua, Padua, Italy, in 1992, and the Ph.D. degree in biomedical engineering from the Polytechnic of Milan, Milan, in 1996.

Since 2005, he has been an Associate Professor of Biomedical Engineering, Faculty of Engineering, University of Padova, where he was a Research Engineer with the Faculty of Medicine from 1997 to 1998 and an Assistant Professor with the Faculty of Engineering from 1999 to 2004. His current research interests include deconvolution and parameter estimation techniques for the study of physiological systems, hormone time-series analysis, and measurement and processing of evoked potentials.



Claudio Cobelli (S'67–M'70–SM'97–F'03) was born in Bressanone (Bolzano), Italy, on Feb. 21, 1946. He received the Doctoral degree (Laurea) in electrical engineering from the University of Padova, Padova, Italy, in 1970.

From 1970 to 1980, he was a Research Fellow of the Institute of System Science and Biomedical Engineering, National Research Council, Padova. From 1973 to 1975, he was an Associate Professor of Biological Systems with the University of Florence, Florence. From 1975 to 1981, he was an Associate Professor of Biomedical Engineering with the University of Padova. In 1981, he became a Full Professor of Biomedical Engineering with the University of Padova. His current research interest includes the field of modeling and identification of physiological systems, especially endocrine metabolic systems. He is the author of around 200 papers in internationally refereed journals. He is coeditor of *Carbohydrate Metabolism: Quantitative Physiology and Mathematical Modeling* (Chichester: Wiley, 1981), *Modeling and Control of Biomedical Systems* (Oxford: Pergamon, 1989), and *Modeling Methodology for Physiology and Medicine* (New York, NY: Academic, 2000). He is coauthor (with E. R. Carson and L. Finkelstein) of *The Mathematical Modeling of Metabolic and Endocrine Systems* (New York, NY: Wiley, 1983) and (with D. Foster and G. Toffolo) of *Tracer Kinetics in Biomedical Research: from Data to Model* (London: Kluwer/Plenum). He is currently Associate Editor of the *Mathematical Biosciences*. He is on the Editorial Board of the *American Journal of Physiology*: *Endocrinology and Metabolism,* and has been in the past on the Editorial Board of the *Control Engineering Practice;* the *Diabetes*, *Nutrition, & Metabolism*; the *Diabetologia;* and the *American Journal of Physiology: Modeling in Physiology*.

Dr. Cobelli is currently an Associate Editor of the IEEE TRANSACTIONS ON BIOMEDICAL ENGINEERING. He has been Chairman (1999–2004) of the Italian Biomedical Engineering Group and has been Chairman (1990–1993 and 1993–1996) of *IFAC TC on Modeling and Control of Biomedical Systems*. He is a member of *International Federation for Medical and Biological Engineering*, *Biomedical Engineering Society*, *Society for Mathematical Biology*, *American Diabetes Association*, and *European Association for the Study of Diabetes*.