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Modeling the Error of Continuous Glucose Monitoring Sensor Data: Critical Aspects Discussed through Simulation Studies

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Abstract

Background:

Knowing the statistical properties of continuous glucose monitoring (CGM) sensor errors can be important in several practical applications, e.g., in both open- and closed-loop control algorithms. Unfortunately, modeling the accuracy of CGM sensors is very difficult for both experimental and methodological reasons. It has been suggested that the time series of CGM sensor errors can be described as realization of the output of an autoregressive (AR) model of first order driven by a white noise process. The AR model was identified exploiting several reference blood glucose (BG) samples (collected frequently in parallel to the CGM signal), a procedure to recalibrate CGM data, and a linear time-invariant model of blood-to-interstitium glucose (BG-to-IG) kinetics. By resorting to simulation, this work shows that some assumptions made in the Breton and Kovatchev modeling approach may significantly affect the estimated sensor error and its statistical properties.

Method:

Three simulation studies were performed. The first simulation was devoted to assessing the influence of CGM data recalibration, whereas the second and third simulations examined the role of the BG-to-IG kinetic model. Analysis was performed by comparing the "original" (synthetically generated) time series of sensor errors vs its "reconstructed" version in both time and frequency domains.

Results:

Even small errors either in CGM data recalibration or in the description of BG-to-IG dynamics can severely affect the possibility of correctly reconstructing the statistical properties of sensor error. In particular, even if CGM sensor error is a white noise process, a spurious correlation among its samples originates from suboptimal recalibration or from imperfect knowledge of the BG-to-IG kinetics.

continued →

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Abbreviations: (ACF) autocorrelation function, (AR) autoregressive, (BG) blood glucose, (CGM) continuous glucose monitoring, (IG) interstitial glucose, (LTI) linear time invariant, (PACF) partial autocorrelation function, (PSD) power spectral density, (SCGM) simulated continuous glucose monitoring, (SIG) surrogate interstitial glucose

Keywords: blood–interstitium delay, calibration, diabetes, dynamic system, time-series modeling

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Abstract cont.

Conclusions:

Modeling the statistical properties of CGM sensor errors from data collected *in vivo* is difficult because it requires perfect calibration and perfect knowledge of BG-to-IG dynamics. Results suggest that correct characterization of CGM sensor error is still an open issue and requires further development upon the pioneering contribution of Breton and Kovatchev.

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Introduction

Continuous glucose monitoring (CGM) sensors allow collecting 7–14 days of information about glucose fluctuations and are recognized to be potentially very useful in the management of diabetes. In particular, several applications of CGM sensors, either in real time or retrospective, demonstrated that their use can improve glycemic control, e.g., by reducing glucose variability and occurrence of hypo/hyperglycemic episodes.[1–4]

As any measurement system, CGM sensors are affected by unpredictable errors. Tools such as continuous glucose–error grid analysis are largely employed to quantitatively assess the accuracy of CGM sensors.[5] In several situations, including real-time filtering and prediction[6,7] and in the designing and testing (possibly *in silico*) of closed-loop controllers,[8–10] there is the need of a more sophisticated description of sensor errors. In particular, the time series of sensor errors should be naturally modeled as the realization of a stochastic process.

Providing a quantitative model of the stochastic process generating CGM sensor errors is difficult for both experimental and methodological reasons. First of all, (some tens of) blood glucose (BG) samples, collected frequently in parallel to CGM, are needed as a reference. However, the use of BG references is not straightforward. In fact, because CGM sensors respond to interstitial glucose (IG) and not directly to BG, a model of the BG-to-IG dynamics is needed to account for signal distortion. Finally, calibration also comes into play. In fact, CGM sensors measure a current electrical signal whose conversion in glucose concentration may also be affected by errors.[11–13] State-of-the-art of modeling sensor error time series is discussed in the next section, together with the discussion of some critical points, later specifically addressed by simulation.

Modeling of CGM Sensor Error

State of the Art

Only a few papers have explicitly considered the problem of modeling the time series of CGM sensor errors. Chase and colleagues,[14] after having pointed out that no studies about sensor error were previously available, proposed to model sensor errors in the simplest way, i.e., a random white noise Gaussian process with a constant coefficient of variation. Breton and Kovatchev[15] proposed a more sophisticated model, where sensor error is not white and also non-Gaussian. In particular, after analysis of a data set from 28 type 1 diabetic subjects consisting of both CGM data (1-minute sampling) and BG references measured frequently in parallel (15-minute sampling), they concluded that the time series of the reconstructed CGM sensor errors can be described as realization of the output of an autoregressive (AR) filter of order 1 driven by white noise. The procedure adopted[15] included two major steps: (a) CGM data were recalibrated by fitting a linear regression model against all the available BG references[16] and (b) in order to take into account distortion due to BG-to-IG dynamics, data fit incorporated the linear time-invariant (LTI) model of BG-to-IG kinetics proposed elsewhere.[17] Notably, in step b, a "population" value of the time constant τ of the model of BG-to-IG kinetics was determined and used for all the 136 individuals of the data set. The average autocorrelation function (ACF) and the average partial autocorrelation function (PACF) were then employed to assess the estimated sensor error time series and its statistical properties.

The contribution of Breton and Kovatchev[15] is very important because, for the first time, the role of calibration and BG-to-IG distortion has been explicitly considered.

However, the consequence of some of their assumptions on the finally derived model deserves attention. In fact, two assumptions of their modeling approach, i.e., perfectly recalibrated CGM data are obtained in step a and perfect knowledge of a LTI model of BG-to-IG kinetics is made available in step b, are critical and can severely affect the outcome of the analysis. As far as step a is concerned, the recalibration method[16] improves CGM data calibration, but is not able to provide perfectly recalibrated data, e.g., it cannot deal with a possible time variance of the calibration parameters. Concerning step b, assuming that BG-to-IG kinetics is linear and time invariant for several days, as done implicitly by employing the LTI model of Rebrin and colleagues,[17] is an unlikely assumption. Furthermore, assuming that parameter τ of the model of BG-to-IG dynamics is set to a "population" value does not allow dealing with the interindividual variability of BG-to-IG dynamics, an accepted fact also evidenced, on a subset of the same database, in Facchinetti and associates.[18]

Aim

The aim of this work was to show that the aforementioned assumptions have a serious influence on the quantitative results provided elsewhere.[15] In particular, three simulation studies were performed. The first simulation was devoted to assessing the influence of CGM data recalibration. The second and third simulations allowed examining the role of the BG-to-IG kinetic model. Analysis was performed by comparing the "original" (synthetically generated) time series of sensor error versus its "reconstructed" version in both time and frequency domains. We showed that even small errors either in CGM data recalibration or in the description of BG-to-IG dynamics can severely affect the possibility of correctly reconstructing the statistical properties of the time series of sensor errors accordingly to the procedure proposed by Breton and Kovatchev.[15] In particular, even if the "true" (synthetically generated) time series of CGM sensor error is a white process, a spurious correlation among the samples of its "reconstructed" version originates from suboptimal recalibration or from imperfect knowledge of the BG-to-IG kinetics.

Methods

Three simulation studies were performed. The first simulation was devoted to assessing the influence of CGM data recalibration, whereas the second and third simulations examined the role of the BG-to-IG kinetic model. Analysis was performed by comparing the "original" (synthetically generated) time series of sensor errors vs its "reconstructed" version in both time and frequency domains.

Role of Imperfect Calibration

To better grasp some practical problems of CGM data calibration, **Figure 1** shows data (BG measurements denoted by red stars, CGM output denoted by blue line) of 1 of the 28 subject data sets.[15] The two signals are expected to be different because of the low-pass filtering distortion due to BG-to-IG dynamics. However, a calibration problem is also present. In particular, there is a mismatch in the "average" levels in the interval centered on hour 10 and, again, in a second interval centered on hour 31. Intuitively, an efficient (re)calibration procedure should compensate a systematic overestimation in the first interval and a systematic underestimation in the second one. In this case, trying to compensate calibration errors of different signs by multiplying the entire time series by a single scale factor, such as the method[16] used in Breton and Kovatchev,[15] is obviously suboptimal and cannot lead to perfectly calibrated CGM data.

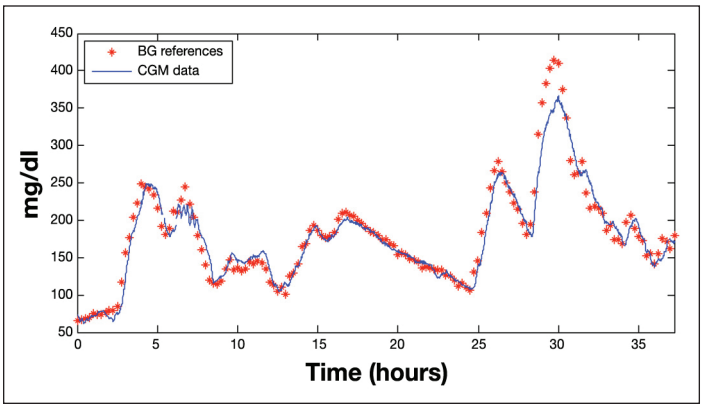

Figure 1. Representative subject data set.[15] BG references (red stars) vs CGM data (blue line) profiles.

Using simulation, the original sensor error statistics can be distorted because of inaccurate (re)calibration. Using the frequently collected samples of BG in 1 of the 28 type 1 subjects of Breton and Kovatchev,[15] we generated, by a smoothing spline procedure,[19] a continuous profile BG(t). Then, by numerically integrating the LTI differential equation describing the BG-to-IG model

$$\dot{IG}(t) = -\frac{1}{\tau} IG(t) + \frac{g}{\tau} BG(t) \quad (1)$$

the IG concentration has been obtained. In this specific study, the static gain of system g has been considered equal to 1 and the time constant τ = 20 minutes (both values are mean values obtained in the BG-to-IG model identification study of Facchinetti and colleagues[18]).

Then, in order to simulate a noisy CGM time series, the IG profile is multiplied by a random time-varying "calibration error" s(*t*) and then corrupted by an additive sequence sampled from a zero mean white Gaussian noise process v(*t*) with variance σ^2, obtaining

$$SCGM(t) = (1 + s(t))IG(t) + v(t), \quad (2)$$

where SCGM(*t*) is the simulated CGM output at time *t*. The way in which the SCGM profile is created closely resembles the formulation proposed elsewhere.[20] Notably, when s(*t*) = 0, SCGM results "optimally calibrated." The calibration error s(*t*) has been created using a triple integrator of a zero mean white noise w(*t*)

$$s(t + 1) = 3s(t) - 3s(t - 1) + s(t - 2) + w(t). \quad (3)$$

Examples of realization of 1-day profile s(*t*) are reported in **Figure 2** (blue line). Of note is that the maximum excursion is of the order of 10% of the reference value. This situation corresponds to a calibration error condition similar to that reported in **Figure 1**. It is worth noting that the model of **Equation (3)** assumes that s(*t*) is zero mean. This assumption can be taken without any loss of generality because introduction of a bias term would make the results of our analysis even worse.

Finally, both BG and SCGM time series have been (under)sampled every 15 minutes in order to reproduce the study conditions of Breton and Kovatchev.[15] Data of a representative synthetic data set are shown in the first row of **Figure 3**. Here, a value of $\sigma^2 = 4$ mg^2/dl^2 was considered, according to considerations reported elsewhere[21] (however, the σ^2 value is not critical, and identical results could be obtained, e.g., by doubling or halving it). The left side of **Figure 3** shows an 8-hour window of simulated BG (red), IG (green), and SCGM (blue) time series. In the same 8-hour window, the right side of **Figure 3** displays the original sensor error, v(*t*) in **Equation (2)**, which was added to IG to simulate CGM data.

To reconstruct the sensor error time series v(*t*) with the procedure of Breton and Kovatchev,[15] we first recalibrated[15] SCGM data by exploiting the linear regression model.[16] Then, we compared the obtained profile with the so-called surrogate interstitial glucose (SIG) profile,[16] obtained by integrating **Equation (1)**, using BG references as input and using the "true" value of τ (i.e., we assumed perfect knowledge of the BG-to-IG dynamics and no measurement error on BG references).

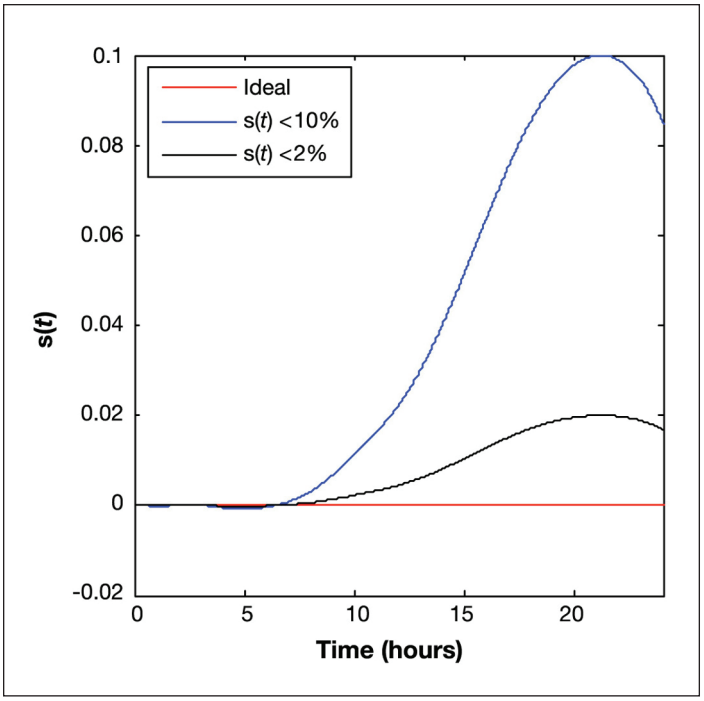

Figure 2. Simulated time-varying calibration error s(*t*). Ideal condition is the red line, and calibration error realizations with maximum excursion equal to 10 and 2% of the reference value are blue and black lines, respectively.

SIG represents the "best" reconstruction of IG possible to obtain starting from BG references and a model of the BG-to-IG kinetics.[17] Because no error on the BG-to-IG model is assumed, SIG corresponds exactly to IG in this first simulation. According to Breton and Kovatchev,[15] the difference between these two profiles (i.e., SCGM and SIG) is the "reconstructed" version of the time series of the sensor errors v(*t*).

Role of Imperfect Description of BG-to-IG Kinetics: Error in τ

The aim of the second simulation was to show that the original sensor error statistics can be distorted when the parameter τ of the LTI BG-to-IG model of **Equation (1)** is not exact, e.g., either because it was estimated with some errors from data (unavoidable in practice) or because a population, rather than an individually tuned, value was used.

Data were generated as in the previous subsection, with the only difference that no calibration error was present [s(*t*) = 0 and, as a consequence, the recalibration step was no longer necessary]. Data of the representative subject are shown in the first row of **Figure 4** (note that the same error sequence of **Figure 3** is used).

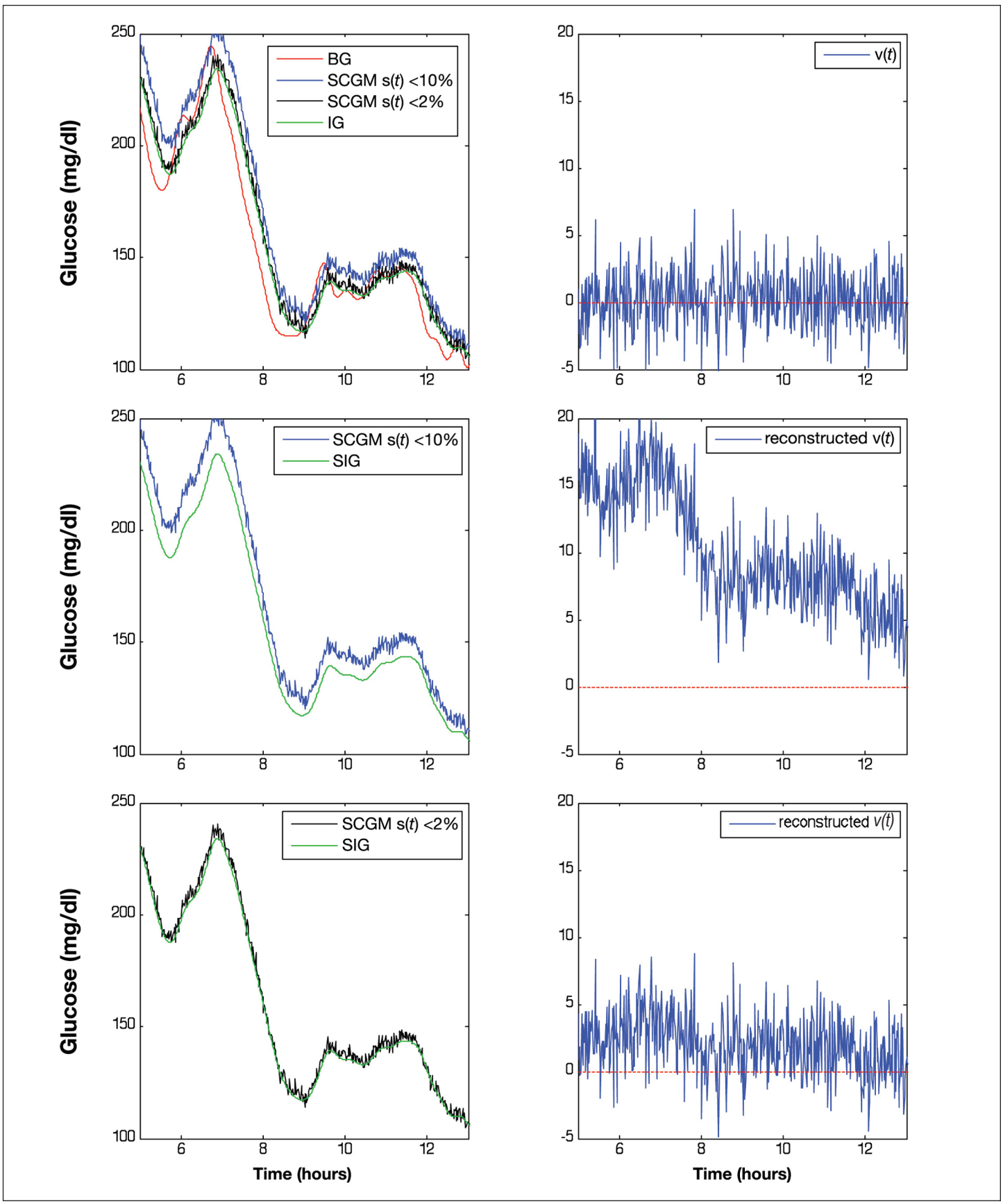

Figure 3. Simulation of time-varying calibration error. First row—Left: true BG (red), IG (green), SCGM with s(*t*) <10% (blue), and SCGM with s(*t*) <2% (black) profiles. Right: true time series of sensor errors. Second row—Left: model fit of SIG (green) vs SCGM with s(*t*) <10% (blue). Right: reconstructed time series of sensor errors. Third row—Left: model fit of SIG (green) vs SCGM with s(*t*) <2% (black). Right: reconstructed time series of sensor errors.

In this case, we studied the influence of using, in the procedure aiming at reconstructing the sensor error, a (slightly) incorrect value, i.e., 18 instead of 20 minutes, of parameter τ of **Equation (1)** characterizing the BG-to-IG kinetics. It is important to emphasize that the simulated error on τ (2 minutes) is lower than the intraindividual and interindividual variability of this parameter found on real data.[18] Model fit and reconstructed sensor error time series are displayed in the second row of **Figure 4**.

Role of Imperfect Description of BG-to-IG Kinetics: Time Variance of τ

Finally, the third simulation considered BG-to-IG dynamics governed by **Equation (1)**, where τ is a function of time, i.e., $\tau = \tau(t)$. This situation describes a possible intra-individual variability of BG-to-IG kinetics, very likely occurring in multiple-day CGM monitoring. In this simulation, τ was modeled as a sinusoidal oscillation

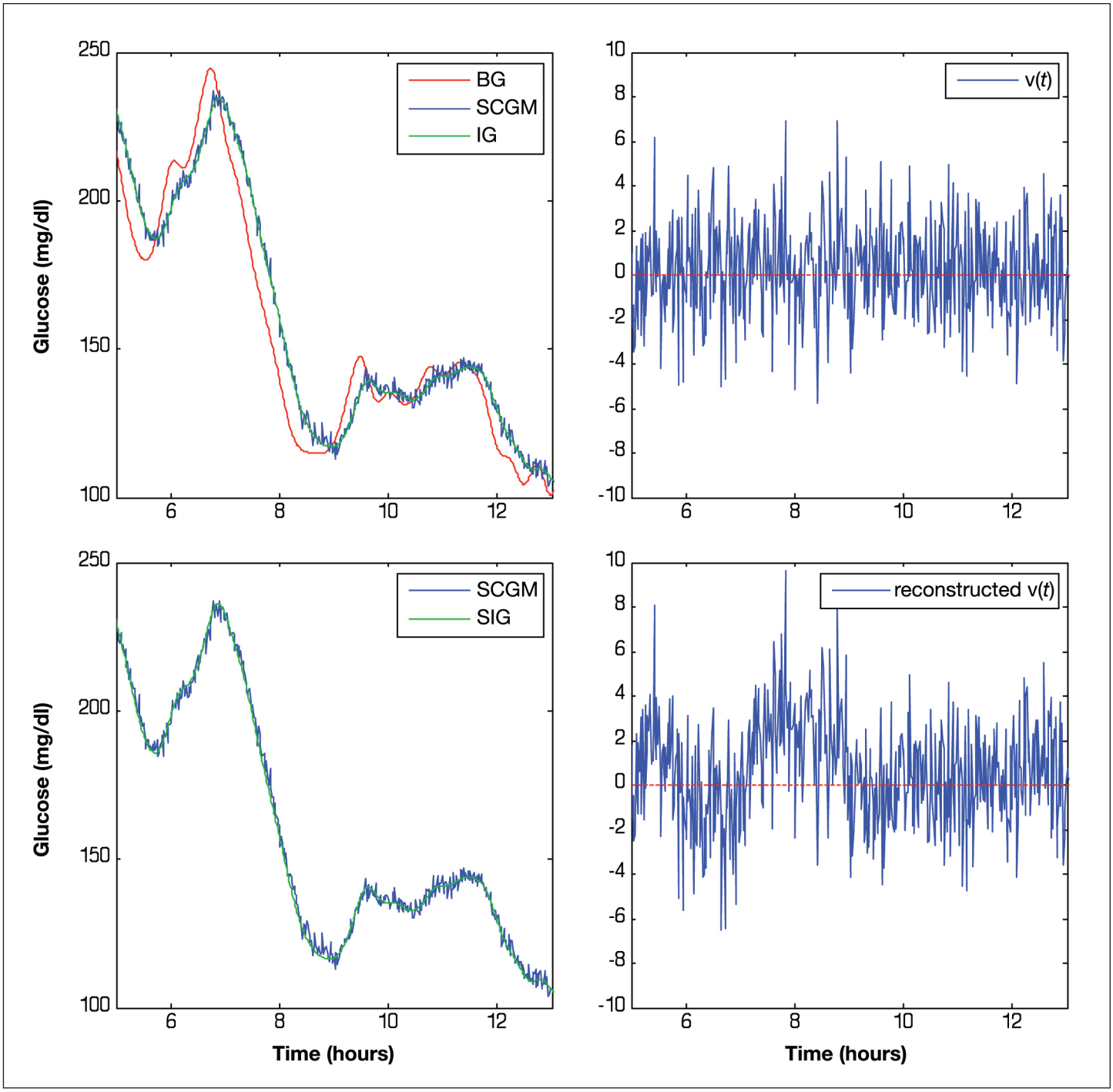

Figure 4. Simulation of uncertainty of τ. First row—Left: true BG (red), IG (green), and SCGM (blue) time series. Right: true time series of sensor error. Second row—Left: model fit of SIG (green) vs SCGM (blue). Right: reconstructed time series of sensor error.

(with maximum amplitude of 2 minutes and a period of 1 day) centered on a mean value of 20 minutes. As in the previous simulation, SCGM data error was assumed to be white and no calibration error was considered. Data of the representative subject are shown in **Figure 5** (first row). In order to reconstruct sensor errors, SIG was fitted against the SCGM profile using a LTI BG-to-IG model (second row of **Figure 5**, left).

For all three simulations, in order to characterize the statistical properties of the original and estimated sensor errors on the whole data set, both ACF and PACF have

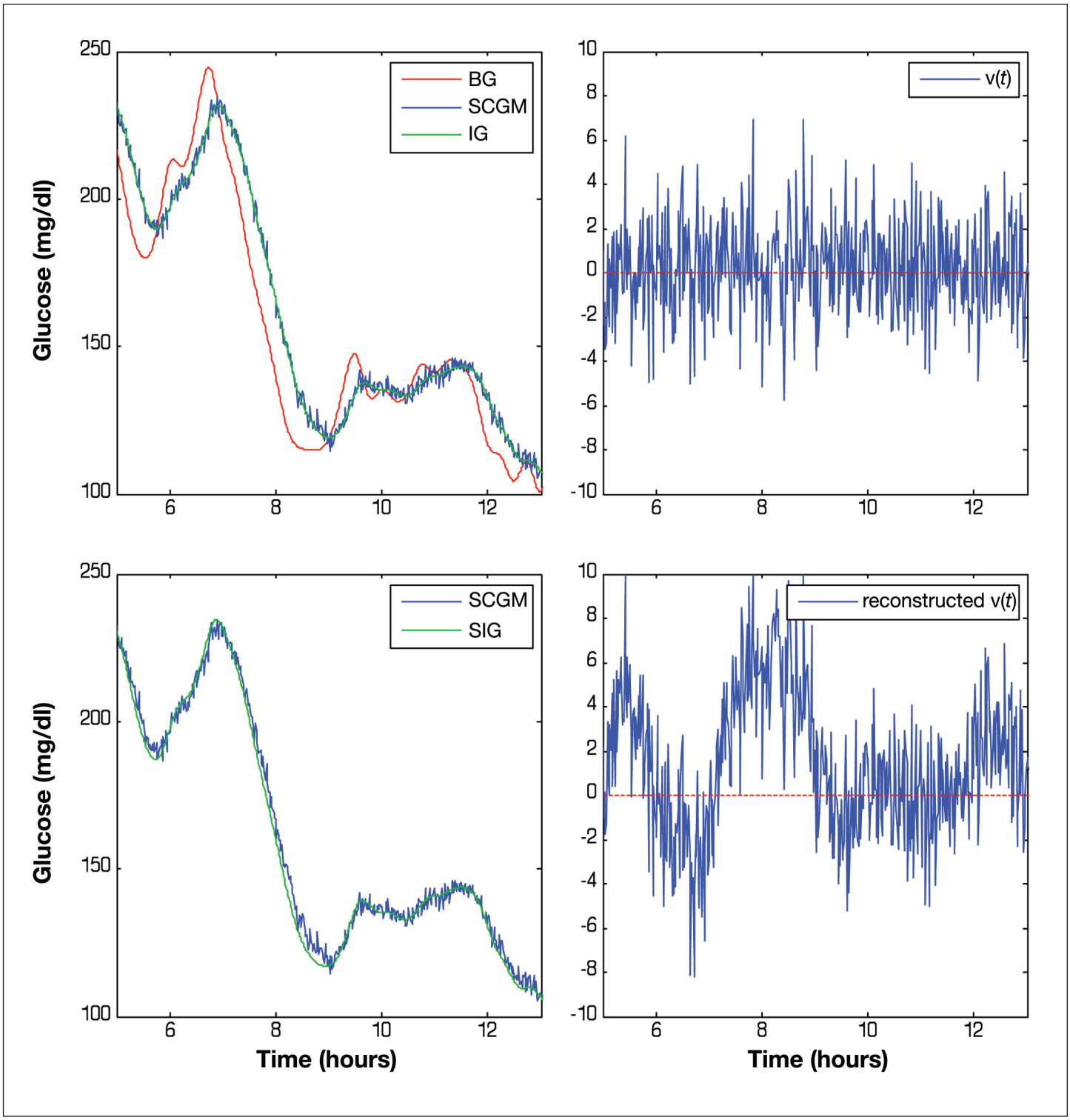

Figure 5. Simulation of time variance of τ. First row—Left: true BG (red), IG (green), and SCGM (blue) time series. Right: true time series of sensor error. Second row—Left: model fit of SIG (green) vs SCGM (blue). Right: reconstructed time series of sensor error.

been assessed, as in Breton and Kovatchev.[15] In addition, the average power spectral density (PSD) was computed.

Results

Role of Imperfect Calibration

Results in the time domain are shown in the second row of **Figure 3**. The left side of **Figure 3** shows the comparison between SIG (green) and SCGM (blue) time series. The right side of **Figure 3** displays the reconstructed sensor error v(*t*). Even with perfect knowledge of the BG-to-IG model, the original and reconstructed time series of sensor errors look very different. In particular, despite the use of recalibration as in Breton and Kovatchev,[15] the effect of calibration error was not eliminated completely: the time series of the reconstructed v(*t*) (second row, right) has a mean value of 11.9 mg/dl and a very visible low-frequency component.

Results in the frequency domain on original and reconstructed v(*t*) are reported in the first and second rows of **Figure 6**, respectively. Left, middle, and right sides of **Figure 6** show ACF, PACF, and PSD, respectively (in both ACF and PACF plots, a time lag corresponds to 15 minutes). While "true" sensor error time series lead to ACF, PACF, and PSD typical of white noise processes (first row), the "reconstructed" sensor error time series (second row) have quite different characteristics. In fact, the ACF plot shows a significant correlation until time lag = 10 (150 minutes), PACF shows that most of the correlation can be attributed between two samples that are distant only 1 time lag, and, finally, the PSD plot is very different from the likely constant spectrum of the white noise; in addition, the PSD shows that a spurious low-frequency component has been introduced.

Are these encouraging results a consequence of a too large calibration error? Similar results were attained by reperforming the simulation by reducing the maximum excursion of s(*t*) to 2% of the reference value (fivefold bias reduction, see **Figure 2**, black line). The left side in the first row of **Figure 3** shows the new SCGM output (black line) in the same representative subject. The left and right sides in the third row of **Figure 3** illustrate, in the same 8-hour window, the comparison between SIG (green) and SCGM (black) profiles and the reconstructed v(*t*), respectively. Also, in this case the reconstructed v(*t*) is quite different from the original, with a mean value of 2.4 mg/dl. Looking at ACF, PACF, and PSD plots (third row of **Figure 6**), similar results were found for the previous simulation hold, including the presence of an elevated correlation and a low-frequency component.

Results of ACF, PACF, and PSD of these two simulations show that even if the original error has a "white" spectrum, the estimated sensor error has a "colored" spectrum. In particular, referring to the PACF analysis made in Breton and Kovatchev,[15] the estimated sensor error can be modeled as an AR process. As a consequence, even when small (maximum 2%) time-varying calibration errors are present, the time series of sensor errors v(*t*) cannot be modeled using the methodology proposed in Breton and Kovatchev.[15]

Qualitatively identical results can be obtained by generating synthetic data starting from any of 28 subjects of the data set.[15]

Role of Imperfect Description of BG-to-IG Kinetics: Error in τ

By looking at the time-domain results in **Figure 4**, even if SIG and IG profiles are quite close (left), the time series of reconstructed sensor error (second row, right) differs significantly from that of the true one (first row, right). For instance, the excursion range is modified and, as evident from **Figure 6** (fourth row), a significant spurious autocorrelation is detectable. In particular, the ACF plot shows a significant correlation until time lag = 3 (45 minutes), and, by looking at the PACF plot (middle), most of the correlation can be attributed at two sampled distant 1 time lag. The spurious low-frequency component is rather evident in PSD, with a peak at a time period of T = 4 hours. Interestingly, while the time series of the true synthetically generated sensor error is white noise, the time series of the reconstructed sensor error can be modeled (according to the PACF analysis of Breton and Kovatchev[15]) as an AR process of order 1 (as in the previous subsection). This demonstrates that even in the presence of perfect calibration, a small error in parameter τ (due to either uncertain estimation from real data or use of a population instead of an individual value) influences the results of the methodology proposed in Breton and Kovatchev.[15]

Role of Imperfect Description of BG-to-IG Kinetics: Time Variance of τ

As expected, parameter identification returned the average value τ = 20 minutes. Visual inspection of the reconstructed time series of the sensor error (second row of **Figure 5**, right) and its statistical analysis by ACF, PACF, and PSD (fifth row of **Figure 6**) allow us to draw results very similar, also quantitatively, to those of the previous subsection. Notably, the PACF plot in the middle section of **Figure 6** suggests that sensor error can

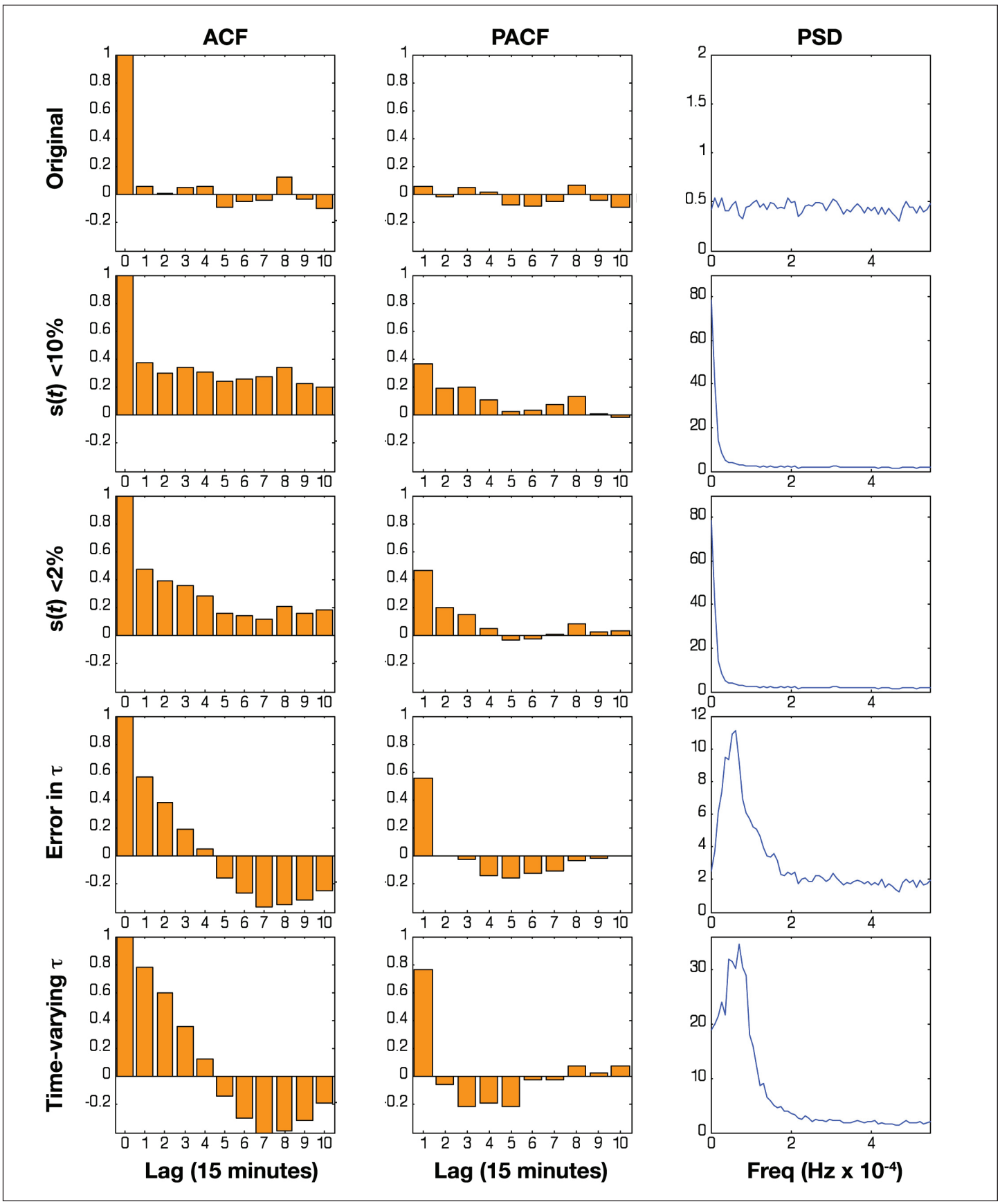

Figure 6. ACF (left), PACF (middle), and PSD (right) of true sensor error time series (first row) and of reconstructed sensor error time series: s(*t*) <10% (second row); s(*t*) <2% (third row); error in τ determination (fourth row); time-varying τ (fifth row). Freq, frequency.

be modeled as an AR process of order 1. Again, a wrong conclusion on the structure of the time series of sensor error was drawn because of small deviations from the ideal assumptions required by the method of Breton and Kovatchev.[15]

Conclusions

Knowing the statistical properties of the time series of CGM sensor error is important in several practical applications. For instance, in a denoising and prediction context,[6,7] the theory of optimal filtering requires a second-order statistical description of measurement errors.[22] Also, having a model of sensor error can be useful in the design and implementation of both open- and closed-loop glucose control algorithms.[8–10] Unfortunately, obtaining a reliable model of the time series of CGM sensor error is difficult and, not surprisingly, only a few contributions are found in the literature. Among them, the work by Breton and Kovatchev[15] has pointed out two fundamental aspects: experimentally, there is the need to collect, in addition to CGM data, several BG references at high-frequency sampling; and methodologically, both distortions introduced by BG-to-IG dynamics and problems of CGM data recalibration must be taken into account. Methodological challenges are, however, still open. As demonstrated in our work, even small errors in any of the aforementioned components can significantly modify the original statistics of the sensor error. In particular, we have shown by simulation that the first-order AR model they obtained[15] could describe spurious low-frequency components in the reconstructed time series of sensor error introduced by either a deficient recalibration or an imperfect BG-to-IG kinetics description. In other words, what was possible to describe with a first-order AR model was due to error in modeling, not to a randomly generated error within the sensor.

Future developments of methodologies to reliably model time series of sensor error probably need to start with sophistication of the recalibration algorithms in order to deal with the possible time variance of the calibration factor during multiple day monitoring. Also, in order to avoid dealing with the inherent difficulties of describing BG-to-IG kinetics and its possible interindividual and intraindividual variability, suitable *in vitro* studies may be designed where reference and CGM are measured in parallel without any distortion.

In the end, it is worth remembering that calibration and BG-to-IG kinetics are probably the major sources of error affecting the accuracy of CGM readings, but other sporadic events, e.g., motion artifacts, loss of sensitivity of the sensor, or the inflammatory response, should also be considered and possibly integrated into a model of sensor error.

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