Kalman Smoothing for Objective and Automatic Preprocessing of Glucose Data

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***Abstract*— A method for preprocessing a time series of glucose measurements based on Kalman smoothing is presented. Given a glucose data time series that may be irregularly sampled, the method outputs an interpolated time series of glucose estimates with mean and variance. The method can provide homogenization of glucose data collected from different devices by using separate measurement noise parameters for differing glucose measurement equipment. We establish a link between the ISO 15197 standard and the measurement noise variance used by the Kalman smoother for Self Monitoring of Blood Glucose (SMBG) measurements. The method provides phaseless smoothing, and it can automatically correct errors in the original datasets like small fallouts and erroneous readings when surrounding data allows. The estimated variance can be used for deciding at which times the data are trustworthy. The method can be used as a preprocessing step in many kinds of glucose data processing and analysis tasks, such as computing the Mean Absolute Relative Deviation (MARD) between measurement systems, or estimating the plasma-to-interstital fluid glucose dynamics of continuous glucose monitor (CGM) or Flash Glucose Monitor (FGM) signals. The method is demonstrated on SMBG and FGM glucose data from a clinical study. A Matlab implementation of the method is publicly available.**

I. Introduction

DIABETES is a disease suffered by close to 10% of the world's adult population [1].

To avoid the acute and chronic consequences of diabetes, the blood glucose level should be controlled to a level as close as possible to the normal range. To achieve such control, people with diabetes need to measure their blood glucose level frequently.

Blood glucose is most often measured using Self Monitoring Blood Glucose (SMBG) meters. These devices provide discontinuous blood glucose readings, by analyzing a drop of blood that the user applies to a test strip. Advances in sensor technology has resulted in Continuous Glucose Monitor (CGM) systems, which measure the interstitial fluid (ISF) glucose continuously with a thin electrochemical sensor inserted under the skin, and reporting a filtered measurement value usually every 5 minutes. A recent addition to the family of glucose devices is the Flash Glucose Monitor (FGM) [2], that provides data only when the sensor is scanned, but then it provides a current glucose estimate and 8 hours of historic 15-minute interval data, thus providing a kind of hybrid between the two data types.

Tremendous amounts of glucose data are generated with such devices, both in research projects, commercial product development and by far the most data are generated in normal use of the devices by individual users.

Errors are present in most glucose data sets, and include sensor system errors and user errors. For SMBG systems a common source of error is incorrect sampling procedure [3], e.g. forgetting to clean the finger before sampling. There is also a baseline variation caused by strip manufacturing variability. For CGM systems, pressure induced sensor attenuation (PISA) errors are common [4], [5], usually resulting from the patient lying on the sensor. Fallouts, bias and latencies are other occurences in CGM data [6], and some or all of these errors also apply to FGM.

The primary purpose of SMBGs and CGMs is to provide real-time information about glucose levels, allowing the user to take informed decisions about insulin dosing, meals and exercise, thus helping to avoid hyper- and hypoglycemia. There are many possible secondary uses of the glucose data in offline settings. One possibility is to estimate the parameters of glucose-insulin metabolism models, which has been of interest to many, see e.g. [7]–[10], thereby obtaining personalized models of the glucose-insulin system. Such models have many uses, for instance in model predictive control (MPC) of an artificial pancreas (AP), see e.g. [11]. Since estimates of model parameters will suffer from noisy or erroneous measurements [12], data should be cleaned and smoothed before parameter estimation commences.

Mean Absolute Relative (MARD) analysis is commonly used to characterize and compare sensor systems. This analysis is also sensitive to errors in the data sets, and to some researchers it is useful to be able to detect outliers in the reference signal, typically SMBG or laboratory measurements. MARD analysis can also require interpolation in order to be able to properly align data points between the different sensor systems.

This paper proposes a preprocessing method for interpolation of glucose data and suppression/removal of outliers in an automatic and objective manner. The methods based on

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Kalman smoothing, and converts a time series of possibly irregularly spaced blood glucose measurements to a continuous time series of interpolated estimates with mean and variance (uncertainty). The method is able to cater for different measurement devices by using device-specific noise models. The method can also cater for other glucose dynamics models than those presented here, including models with person-specific parameters.

The presented method is suitable for homogenizing glucose data sets, which is valuable in an offline automated data processing setting to increase data yield. The method also provides a consistent interpolation between glucose values without introducing interpolation artefacts like those that may result from other methods, e.g. cubic spline interpolation. Since the smoothing is applied in a forward-backward manner, a phaseless smoothing and interpolation of the noise data is achieved. Finally, the method takes into account the uncertainty of the measurements, which can be used to determine which parts of the measurement series are trustworthy and which are not.The method was originally intended for processing SMBG data, but is extendable to include CGM/FGM data as well, which is demonstrated. The method is tested on real SMBG and FGM glucose data from a clinical study. This paper expands on ideas previously presented in [13].

The key contributions of this paper are:

- Use of Kalman smoothing applied to glucose data, resulting in phaseless smoothing and interpolation.
- Glucose data interpolation with realistic uncertainty estimates
- Derivation of a measurement noise model from ISO 15197:2015 [14] for SMBG measurements.
- Possibility of combining glucose data sources with different noise characteristics

II. Method

In this section Kalman filtering and fixed-interval Kalman smoothing is revisited, and their application to glucose data is described.

A. Kalman filtering

The Kalman filter theory assumes that the signal $\mathbf{y}_k$ to be filtered is generated by a system on the form

$$\mathbf{x}_{k+1} = \mathbf{f}(\mathbf{x}_k, \mathbf{u}_k) + \mathbf{v}_k \tag{1}$$

$$\mathbf{y}_k = \mathbf{h}(\mathbf{x}_k, \mathbf{u}_k) + \mathbf{w}_k \tag{2}$$

Here $\mathbf{x}$ is the system internal state, $\mathbf{u}$ is the input to the system, and $\mathbf{y}$ is the measured output, $\mathbf{v}$ is the process noise, and $\mathbf{w}$ is the measurement noise. These noise processes are assumed to be white, zero mean Gaussian, with covariance given by matrices Q and R, respectively:

$$\mathbf{v}_k \sim \mathcal{N}(0, Q) \qquad \mathbf{w}_k \sim \mathcal{N}(0, R) \tag{3}$$

The Kalman filter computes a state estimate $\hat{\mathbf{x}}$ and a state covariance matrix $\hat{P}$ for each time step. The system model in Eq. (1) is used to predict the state one step ahead in time. This is called the *time update*, and it results in an *a priori estimate* denoted by $\bar{\mathbf{x}}$ and $\bar{P}$. Then the *measurement update* is performed. This updates the a priori estimate with a measurement with known measurement noise, to produce an *a posteriori estimate* $\hat{\mathbf{x}}$ and $\hat{P}$. In glucose data sets it is commonly the case that measurements are infrequent and/or taken with irregular intervals. The filter handles this by doing several time updates per measurement update. In time steps where no measurement is available, the a posteriori estimate is set equal to the a priori estimate. The Kalman filter equations are [15]:

$$\bar{\mathbf{x}}_k = \Phi_{k-1}\hat{\mathbf{x}}_{k-1} + B_{k-1}\mathbf{u}_{k-1} \tag{4}$$

$$\bar{P}_k = \Phi_{k-1}\hat{P}_{k-1}\Phi_{k-1}^T + Q_{k-1} \tag{5}$$

$$K_k = \bar{P}_k H_k^T (H_k \bar{P}_k H_k^T + R_k)^{-1} \tag{6}$$

$$\hat{\mathbf{x}}_k = K_k(\mathbf{y}_k - H_k\bar{\mathbf{x}}_k) \tag{7}$$

$$\hat{P}_k = (I - K_k H_k)\bar{P}_k \tag{8}$$

Φ is the state transition matrix and H is the measurement matrix. If the system and/or measurement equations are nonlinear, these matrices will in general be time-variant, and can be found from linearizing $\mathbf{f}$ and $\mathbf{h}$ in Eqs. (1) and (2) at each time step around the most recent estimate resulting in the Extended Kalman Filter (EKF). Two different sets of linear system equations have been tested in this work, and are described in section II-D. An augmentation of the state space for CGM-SMBG parameter estimation is described in Sec. II-D.3, and this augmentation makes the resulting system nonlinear, necessitating EKF.

B. Kalman smoothing

The Kalman filter described above is suitable for real-time processing of data, as it only uses past data to produce its estimates. In an offline setting, where the whole data set is available, smoothing can be used to get further improvement of the estimates. Smoothing uses all the available data before and after time k to produce the estimate at time k. The Rauch-Tung-Striebel (RTS) algorithm [16] accomplishes this. RTS first makes a forward pass through the data using the normal Kalman filter Eqs. (4-6), storing the sequences of a priori and a posteriori estimates $\bar{\mathbf{x}}_k$, $\hat{\mathbf{x}}_k$ and state covariance matrices $\bar{P}_k$ and $\hat{P}_k$. These are then used as input to a backward pass that computes the smoothed estimates $\hat{\mathbf{x}}_k^s$ and $\hat{P}_k^s$ as follows [15]:

$$C_k = \hat{P}_k \Phi_k \bar{P}_{k+1}^{-1} \tag{9}$$

$$\hat{\mathbf{x}}_k^s = \hat{\mathbf{x}}_k + C_k(\hat{\mathbf{x}}_{k+1}^s - \bar{\mathbf{x}}_{k+1}) \tag{10}$$

$$\hat{P}_k^s = \hat{P}_k + C_k(\hat{P}_{k+1}^s - \bar{P}_{k+1})C_k^T \tag{11}$$

The filtering and smoothing process is illustrated in Fig. 1. The error bands in this figure (and the rest of this paper) are based on 2 standard deviations (SD), approximating a 95% confidence interval under the Gaussian assumption. The SD is the square root of the diagonal element in the $\hat{P}_k^s$ or $\hat{P}_k$ covariance matrix that corresponds to the glucose state. We have used fixed-interval smoothing in all the results reported

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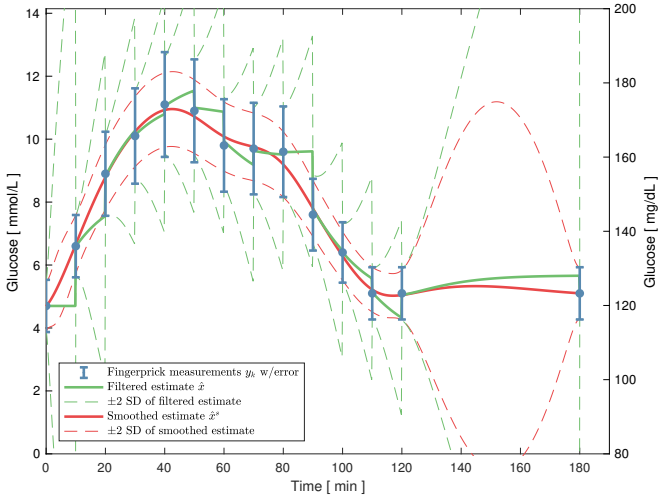

Fig. 1. Filtering vs smoothing in a 3-hr data set of glucose SMBG measurements (blue points, with ISO 15197:2015 error indicated with blue bars). The estimates are shown with solid line for the mean and dashed lines for the 2 SD error band approximating a 95% confidence interval. The forward pass filtering result is shown in green. This estimate is seen to jump every time a measurement arrives, setting a new rate estimate. The smoothed estimate is shown in red. Note how the error of the smoother estimate is smaller than the error bars in the original measurements. This is possible due to the proximity in time of the measurements. In the last hour of the recording the sampling rate is reduced to one sample per hour, and it is seen that the error band of the smoother estimate (red dashed line) grows with time, describing the uncertainty of the estimate during the time of no measurements.

here, utilizing all the available data, i.e. the interval is the entire data set. A fixed-lag smoother implementation would also be possible, where a fixed window of data is used to estimate the state at the start of the window, which is interesting in a near real-time setting.

The error band could be used to determine when it makes sense to use the interpolated values output by the smoother for further analysis, and when the estimates are too uncertain to be used. This could be done by applying a threshold for maximum allowed estimated error band, for example.

C. Noise modeling

An important issue in use of Kalman filtering is the modeling of the noise processes $\mathbf{v}$ and $\mathbf{w}$, more specifically the values of the covariance matrices Q and R.

1) Measurement noise modeling: The measurement noise process $\mathbf{w}$ needs to be set according to which measurement system has generated the data. In a highly accurate laboratory system for blood glucose analysis it is appropriate to use a low variance. If a more inaccurate blood gluose measurement system like an SMBG meter is used, a higher variance on the measurement noise should be used.

The ISO 15197:2015 standard [14] is applicable for SMBG meters, providing limits for measurement error that SMBG manufacturers must comply with. Let us recode these limits into normal distribution variances to be used in the Kalman filter. An SMBG device that conforms to the ISO 15197:2015 standard should have an error within ± 0.83 mmol/L (15 mg/dL) when the real blood glucose level is less than or equal to 5.55 mmol/L (100 mg/dL), and less than $\pm 15\%$ error for higher glucose levels. The standard specifies that 95% of all measurements shall fall within this limit. Interpreting this as a 95% confidence interval the limits correspond to roughly 2 SDs in a normal distribution.

Therefore, to approximate the ISO 15197:2015 measurement variance σ_R^2 we have that $2\sigma_R = 0.83$, i.e. $\sigma_R^2 = 0.172$ [mmol^2/L^2] for measurements below 5.55 mmol/L, and $2\sigma_R = 0.15y$, i.e. $\sigma_R^2 = 0.0056y^2$ for measurement above the limit, where y is the measured glucose value.

The above value(s) for R may serve as conservative defaults if no other information is available. Another value for R could and should be used if more details about the measurement variance is known. Variance information could be found from the following:

- The 2003 version of the ISO 15197 standard has wider limits, so to smooth data from older devices conforming to the old standard, those limits should be used.
- Several SMBG meter manufacturers currently promote their products as having a performance significantly better than the IS015197:2015 limits. For some SMBG devices a more suitable measurement variance may be available from the device documentation.
- In other cases there may be independent analyses of SMBG accuracy that provides information about the error model to use, e.g. as in [17].

2) Process noise modeling: The process noise $\mathbf{v}$ should account for all the noise originating from modeling errors, as well as unknown disturbances affecting the system.

One important point in this context is whether or not meals and insulin injections are considered as inputs or disturbances in the model. For the application considered here, inputless models are preferred. In other words, we treat meals and insulin injections as unknown disturbances to the system. This is done to make the method more generally applicable, since many glucose data sets lack meal and/or insulin information that is accurate enough to be of use in this context.

As a consequence, the variance of the process noise must be set large enough to accomodate glucose excursions originating from meals or insulin injections. Thus, the Q matrix should be chosen such that the error band of the estimate grows quickly enough to envelop worst case glucose excursions, like right after a meal or an insulin injection. This method was used to tune the process noise covariance matrix Q in this work, and is illustrated in Fig. 2. A dataset containing a large meal is used. Those measurements that are most informative about the meal onset have been held back from the smoother. The error band of the estimate (red dashed line in in Fig. 2) grows when measurements are not available, and the growth rate depends on the value of Q. The goal of the tuning is to make the error band conservative enough to encompass the held-back measurements, which represent a worst case glucose excursion from a meal. Since the glucose lowering effect of insulin is comparable to the glucose rising effect of meal digestion [18], we tuned the process noise based on meal cases only.

Values for the Q matrix depend on the unit used to represent glucose by the model, and values given in the following

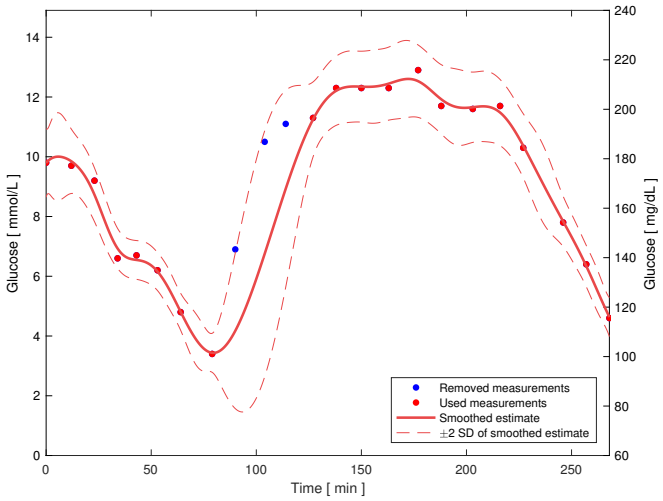

Fig. 2. Illustration of the process noise tuning. Red dots are SMBG measurements available to the smoother, while the blue measurements have been held back.

sections are for models using mmol/L as the unit for the internal state of glucose. The conversion factor from mmol/L to mg/dL is 18.02 and needs to be squared when converting variances.

D. Glucose dynamics modeling

The Kalman filter uses a dynamic model that describes the assumed internal dynamics of the system generating the measurements that are to be filtered. This model is used to provide predictions of the state between each measurement.

Several glucose metabolism models exist in the literature, and research into such models is ongoing. The models range from minimal [19], [20], via intermediate complexity [21]–[24] to maximal models [25], [26]. A common trait in these models is that they require information of the amount of glucose and insulin entering the system, which is not always present in a glucose dataset. When such data are present, they are often erroneous and/or incomplete, unless they have been recorded in strictly controlled research settings.

Another issue with the more complex glucose metabolism models is that they are often non-observable based on glucose measurements alone. This means that the internal state of the model can not be computed based on the measurements. Observability is a requirement for Kalman filtering.

To summarize, the model used in the smoother should be observable and have no external inputs. The two models described below satisfy both these requirements. One is a simple rate-only model, and another is inspired by the model in [24], but further simplified for filtering usage (central-remote rate model). Both models operate without insulin and meal input knowledge.

1) Model 1: Rate-only model: This model is perhaps the simplest dynamic system that could be said to represent glucose. The state vector consists of plasma glucose and its rate, $\mathbf{x} = [G_p \quad \dot{G}_p]^T$, and the model is $\dot{\mathbf{x}} = A\mathbf{x}$ with $A = \left[\begin{smallmatrix} 0 & 1 \\ 0 & -a \end{smallmatrix}\right]$, where a is a small number determining the decay of an observed rate of change. a has been set to 0.05 in this work. Larger values of a will make the rate of change decay faster towards zero. Setting a to zero gives a system where an observed rate of change is allowed to continue indefinitely. This is clearly not physiological and can be detrimental for smoothing performance in data sets where there are long periods of missing measurements.

The system is discretized by setting $\Phi = e^{A\Delta t}$ where the time step Δt has been set to 10 s in this work.

The process noise was set to $Q = \left[\begin{smallmatrix} 0 & 0 \\ 0 & q_{m1} \end{smallmatrix}\right]\Delta t$ for this model, where q_{m1} is a tunable value, set to 0.005 mmol^2/L^2 in this work. It has been found using the worst case analysis described in Sec. II-C.2 and illustrated in Fig. 2. The presence of Δt in the Q matrix is a convenience to automatically adjust the process noise if the discretization time step interval changes.

2) Model 2: Central-remote rate model: In this model, the glucose rate from model 1 is divided into two states, C_c and C_r, where C_c occupies a central compartment, and C_r occupies a remote compartment. In this model, any input (meal/insulin) first affects a central compartment and then with a first order delay diffuses over to the remote compartment where it takes effect on the blood glucose. Another interpretation of the C_c and C_r states is that they describe meal effects when positive, and insulin effects when negative. The effects of any other blood glucose increasing or decreasing phenomena are lumped into the same states.

The state vector of this model is $\mathbf{x} = [G_p \quad C_c \quad C_r]^T$. The state transition equations are

$$\dot{G}_p = C_r \tag{12}$$

$$\dot{C}_c = -\frac{1}{T_d}C_c \tag{13}$$

$$\dot{C}_r = \frac{1}{T_d}(C_c - C_r) \tag{14}$$

where T_d is a parameter of the model, a time constant that describes the rapidness of flow between compartments.

The process noise is set to only directly influence the central compartment, i.e. $Q = \left[\begin{smallmatrix} 0 & 0 & 0 \\ 0 & q_{m2} & 0 \\ 0 & 0 & 0 \end{smallmatrix}\right]\Delta t$. Here q_{m2} is again a tunable parameter, set to 0.02 mmol^2/L^2 in this work, using the same method for finding the process noise level as previously described. The parameter T_d also affects the variance development; the lower the T_d, the faster the process noise on state C_c propagates to C_r. Thus, T_d needs to be tuned together with the process noise, and was set to 600 s in this work. Unless otherwise stated, figures and results in this paper are generated using model 2 as the glucose dynamics model.

3) Plasma-ISF glucose dynamics: An interesting extension to the method presented is possible when both SMBG and CGM measurements are present in the data set to be smoothed.

The smoother described above can be expanded to provide sensor fusion of the two measurement types. Some usage scenarios for such processing include:

- With sparse SMBG and dense CGM data, bias correction of the CGM data is possible
- With dense SMBG and dense CGM data, estimation of person-specific plasma-ISF dynamics is possible in addition to bias
- Improved outlier detection and removal by combining SMBG and CGM data

If SMBG and CGM measurements are both to be used by the smoother, a model describing the plasma-ISF dynamics is needed. Plasma-ISF dynamics has been investigated by several groups, see e.g. [10], [27]–[30]. Preference is here again given to a simple model that do not require other information than the blood glucose and the CGM measured glucose, for observability reasons and for the method to be more generally applicable.

The dynamics between the SMBG and CGM measurements can be modeled by augmenting the glucose dynamics systems described in above sections with a new state G_{isf}, having a first order dynamics relationship to the blood glucose, as in [10]:

$$\dot{G_{isf}}(t) = \frac{1}{T_{isf}}(G_p - G_{isf}) \tag{15}$$

where G_{isf} is interstitial glucose, G_p is plasma glucose, and T_{isf} is the time constant governing the diffusion process. This differential equation can be added to any model that describes the dynamics of G_p (e.g. the ones described in previous sections) to augment them with the ability to use CGM measurements in combination with blood glucose measurements (e.g. SMBG).

To be able to use the CGM measurements, the Kalman filter needs to be expanded to accomodate the extra measurement. One way to do this is to use a two-row measurement matrix H, where the second row measures G_{isf}. In the likely situation that both measurements are not available at the same instant, a better strategy is to only use scalar measurements in the Kalman filter, switching to the appropriate H single-row matrix depending on which measurement is available in a given instant.

A commonly occuring error in CGM measurements are bias errors. This bias can be included in the Kalman filter and estimated as part of the smoothing procedure. The measurement equation becomes:

$$y_{cgm,k} = G_{isf,k} + b_{cgm} + w_{cgm,k} \tag{16}$$

where b_{cgm} is an unknown bias to be estimated, by including b_{cgm} in the state space of the Kalman filter, using zero derivative, zero process noise and a non-zero initial variance that is large enough to describe biases that may be encountered. The zero process noise indicates that the parameter is modeled as an unknown constant. Adding a small noise on the parameter allows it to have some drift; this may also be beneficial for mathematical/numerical reasons to avoid degenerate covariance matrices in the smoothing operation.

The presence of a Gaussian white noise process $w_{cgm,k}$ can be debated. Some researchers have claimed that the CGM measurement noise in CGMs is non-Gaussian, e.g. Breton et al. [28] found that a Johnson distibution was more appropriate. Others argue that inferring the error distribution is confounded by modelling inaccuracies in the plasma-ISF dynamics and/or calibration errors, [31]. As stated in [32], not all CGM systems are equal. Along the lines of the SMBG measurement noise modeling of Sec. II-C.1, we consider the model given by Eqs. (15) and (16) a useful default when no more information is available, and if more detailed information about the CGM errors are available for the data to be smoothed, e.g. as given in [28], [32], [33], these models can be used instead.

The time constant T_{isf} affects the bias estimation, so simultaneous estimation of the bias and the time constant is in order. Thus T_{isf} is also added to the state space in the same fashion as the bias, and estimated by the smoother.

E. Outlier suppression and removal

The method described above works well as is to suppress outliers in the data, due to the smoothing introduced by nearby points.

In some applications outlier suppression is not enough, and it is more desirable to remove the outliers altogether. The described method lends itself to this task, too. The process noise tuning described in Sec.II-C.2 ensures that the error band of the estimate grows rapidly enough to encompass meals and insulin injections. Thus, the error band of the estimate can be used to determine which measurements are likely outliers. This criterium is then well-founded, as it will reject only those measurements that are unlikely based on surrounding data, and taking worst-case, but possible, glucose fluctuations into consideration. We can base such a removal algorithm both on the filter (forward pass) estimate and the smoother (backward pass) estimate.

Outlier detection based on the filter estimate error band is only capable of detecting gross outliers. As discussed above, the process noise used is set relatively high in order to give correct variance development under the assumption that meals/insulin injections may occur at any time. This makes the filter estimate develop a large variance quite quickly after a measurement, as seen in Fig. 1.

Outlier detection based on the smoother estimate error band is more promising. This is intuitively a more sound approach, since also data after the suspected outlier is used to determine if it is an outlier. An example of outlier suppression and removal in a dataset containing a likely outlier is shown in Fig. 5. A block diagram showing the process of filtering and smoothing used for outlier detection is shown in the left side of Fig. 3.

F. Replicate handling

Another case related to outlier removal is a situation that is common in SMBG data sets, where there are two or more measurements close together in time. This may be specified in the study protocol the data has been recorded under, or may be the result of the normal behaviour of some users when they get measurements they believe might be incorrect, repeating a measurement immediately. One such dataset is shown in Fig. 4, where the smoother output is compared to a cubic spline interpolation of the same data. Cubic spline is often used to provide interpolation between points, and the motivation for this comparison is to showcase how risky this can be in an automated setting.

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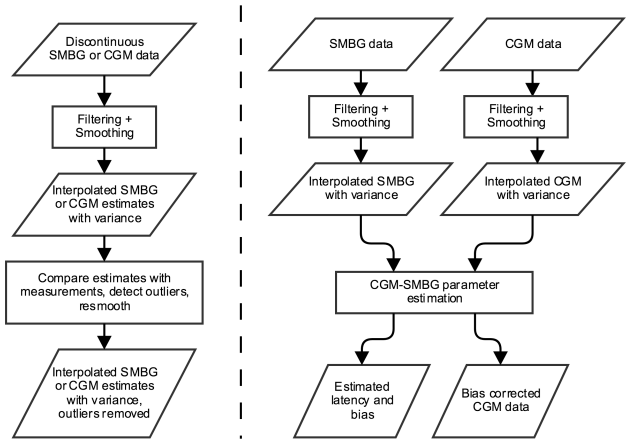

Fig. 3. A block diagram of the interpolation and outlier removal processing (left side) and the data fusion and CGM-SMBG parameter estimation processing (right side)

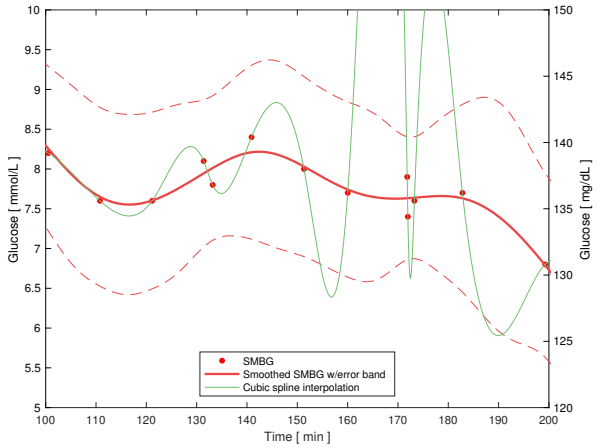

Fig. 4. Automatic handling of triplicates. The smoother estimate (red curve) goes through the mean of the triplicate measurements at t=172 min. A cubic spline interpolation of the same data is shown in green for comparison, where a bad reaction to the proximity in time of the triplicate measurements is seen.

G. Implementation

A Kalman smoother for SMBG measurements and a CGM-SMBG dynamics parameter estimator have been implemented in Matlab, and is publicly available [34]. The estimator uses the smoother individually on the SMBG and CGM measurements, and then uses the resulting smoothed and outlier removed curves to estimate the CGM bias and time constant, as illustrated in the right side of Fig. 3.

H. Testing

The smoother was tested on data sets recorded as reference measurements in a study of BioMKR®, a novel non-invasive glucose sensor being developed by Prediktor Medical, Fredrikstad, Norway. The study was approved by the regional ethical comittee, Study ID: REK Midt 2016/1127.

The study recruited 39 type I diabetes subjects. A calibration session was performed for each subject, where reference glucose was collected every ten minutes with an SMBG meter (Freestyle Freedom Lite, Abbot). A Flash Glucose Monitor (FGM; Freestyle Libre, Abbot), worn on the upper right or left arm, was scanned at the same time as the SMBG measurements were taken. Glucose increase was achieved by sugary drinks, and decreased by insulin injections. The calibration session data sets ranged from 2.6 to 5.8 hours, with a mean duration of 4.6 hours. The SMBG measurements glucose data ranged from 3 to 26 mmol/L, with a mean of 8.5 mmol/L. Only the SMBG and FGM data from the calibration sessions in this study were used as test sets in this paper. The SMBG data were used for testing the smoothing/interpolation and outlier removal.

The approach for combining SMBG measurements and CGM measurements with simultaneous estimation of T_{isf} and b_{cgm} as described in Sec. II-D.3 was tested with synthetic data sets with known time constant and bias. These were generated by simulating the system and measurement Eqs. (15) and (16), using the real SMBG measurements from the calibration sessions as the G_p state and varying T_{isf} (1, 5, 10 and 20 min) and b_{cgm} (-2 to 2 in steps of 0.5). Thus, 36 simulated CGM curves were generated for each of the 39 calibration sessions, resulting in more than 1400 synthetic data sets for testing the parameter estimation, and comparing the estimate with the known true values for the parameters. After using these data sets to determine the smoother's ability to find the parameters, the SMBG-CGM estimator was also tested on the 39 real Freestyle Libre data sets.

III. Results

A. Outlier suppression and removal

Using model 2, the smoother automatically found three outliers in the 39 data sets. One is the dataset shown in Fig. 5, where the point at t=161 min is too high by about 4 mmol/L. The others were too high by about 3 and 2 mmol/L, respectively, and are shown in Fig. 6. Removal of these outliers resulted in a change of MARD between CGM and SMBG measurements of 0.3, 0.7 and 1.5 percentage points for the sets, respectively. This illustrates the impact such outliers in the reference signal can have for subsequent analyses like a MARD computation.

Manual inspection of the other data sets found measurements that could be regarded as more moderate outliers, these are suppressed by the smoother, but not removed.

If instead model 1 was used in the smoother, the result was the same except for one case: the outlier shown in the top panel of Fig. 6 was not removed. It is clear from the figure that this point is just barely outside the error band when using model 2. Model 1 has a slightly faster variance development compared to model 2, making this point fall inside the error band instead of outside, and that is the reason for this point not being labeled an outlier by the smoother when using model 1. This shows that the choice of glucose dynamics model and its process noise parameters can determine the outcome of the outlier removal to some extent.

B. CGM measurement parameter estimation

The SMBG-CGM parameter estimation was run on the synthetic test sets. It estimated the bias to within 0.1 mmol/L

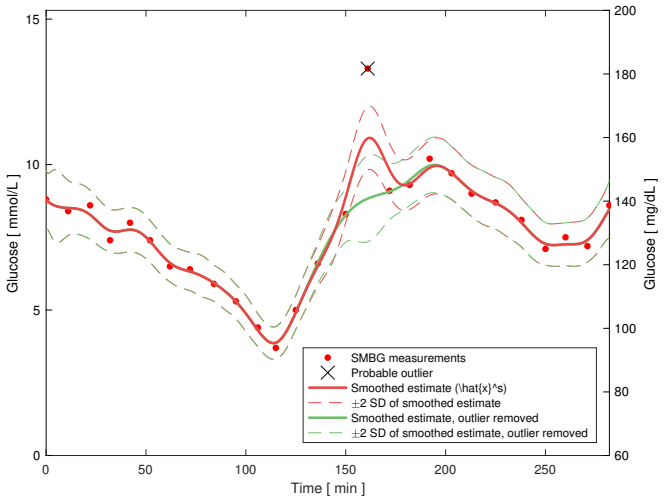

Fig. 5. Outlier suppression and removal. A likely SMBG outlier is present at t=161 min. The surrounding points make the first pass smoother estimate (solid red line) follow a curve that has suppressed the outlier, but the estimate is still drawn towards the outlying value. Removal of outliers can be based on the error band of the smoother (red dashed line). The smoother can be rerun with outliers removed for an improved estimate, this is shown in green. Note how the error band of the resmoothed estimate is now slightly larger where the outlier has been removed.

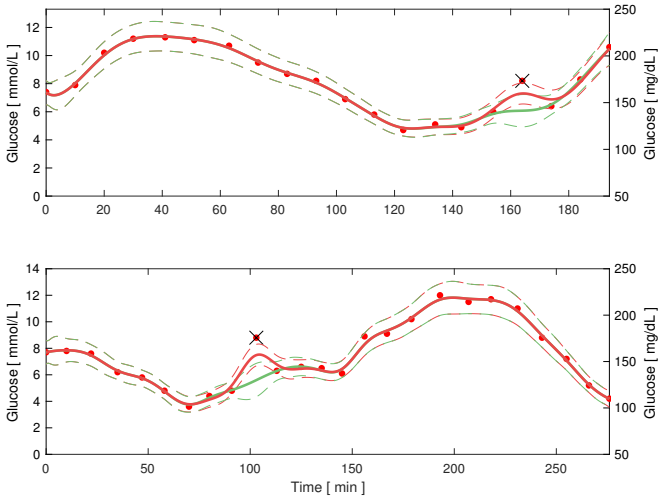

Fig. 6. Two other outliers detected by the method. Legend as in Fig. 5

of the true bias in 95% of the cases with a maximum error of 0.14 mmol/L, and the time constant to within 1 min of the true value in 81% of the cases with a maximum error of 1.8 min.

When run on the real Freestyle Libre data from the 39 data sets from the clinical study, the smoother estimated biases ranging from -1.8 to 1.5 mmol/L and time constants ranging from 1 to 24 min. Parameter estimations are shown for three selected runs in Fig. 7.

IV. Discussion

The Kalman smoothing methods presented here are useful for various tasks in automatic processing of glucose data for research and commercial purposes. The smoother presented is model based, and two simplistic glucose dynamics models

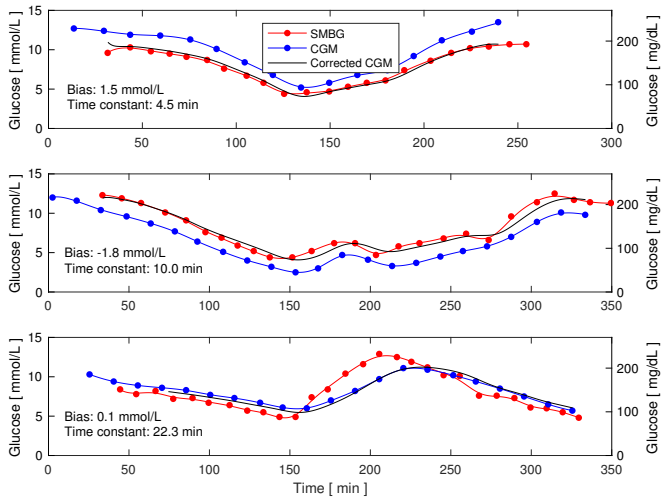

Fig. 7. Parameter estimation of the CGM-SMBG dynamics in three runs from the calibration sets. The three runs display different SMBG-CGM dynamics; the two first sets have clear bias effects in different directions, whereas the last set shows a clear latency effect. Biases and time constants found by the smoother are given in the plots. The black curves are bias corrected CGM signals, produced by retrieving the G_{isf} state after smoothing

were investigated for use in the smoother. The more plausibly the model describes real glucose dynamics, the more confidence we can have that the smoother will give realistic estimates and variances. On the other hand, the model must be observable with glucose as the sole measurement, which limits the complexity of the models that may be used. The choice of model and noise parameter settings gives room for some subjectivity, but it provides a way to be explicit about the assumptions made, which helps provide reproducability.

There are many examples of Kalman filtering applied to glucose in the literature, largely applied in online settings, e.g. for denoising CGM data in real time [35], or for state estimation in MPC settings [11]. Our approach differs in that it uses Kalman *smoothing*. This implies that the method is usable only in offline settings, where all the data is available. Such retrospective settings are common, at least in research, and especially in research related to glucose-insulin metabolism models. One commonly encountered task in metabolism model research is parameter estimation in the models. The importance of smoothing measurement data before attempting state or parameter estimation is acknowledged in [12], where different methods for smoothing glucose data are evaluated. Their optimal segments method is comparable to ours in the resulting curve of smoother estimate means, but lacks the information about the uncertainty in the interpolated signal that our method provides through the estimated variance. This measure of uncertainty is directly useful in a state/parameter estimation setting.

A noteable feature of the output from our smoother is how rapidly the variance grows in periods of no measurements. However, due to the tuning done to encompass worst case glucose fluctuations, this rapid uncertainty development *is realistic* when meal and insulin inputs are considered to be unknown. This feature of our method is useful in SMBG datasets

to get a measure of the uncertainty between measured points, as illustrated in Fig. 1. This enables an informed decision about which interpolated values to include in subsequent analyses.

The strengths of the method include a minimum of assumptions made and high customizability. No person-specific parameters or information about meal and insulin inputs are needed to use the smoother. The method does encode some information about glucose variability and glucose sensor error modeling that could be useful as defaults when no more information is available, and if more detailed information about sensor error, patient glucose dynamics or meal/insulin inputs are available, the method can include this. This includes the use of models with person-specific parameters.

One could also envision clinical use where methods as described here are used to clean and correct SMBG and/or CGM data before they are displayed to users and their caretakers. This could potentially reduce the burden on the users and caretakers in having to know about common errors in the data and trying to mentally correct for them.

The CGM-SMBG parameter estimation implemented as an extended test case in this work finds the correct bias and time constant in synthetic data sets. It finds parameter values in real FGM data sets that are plausible and comparable to those found by other groups for other CGM systems [32], [33] showing that simultaneous estimation of these parameters can be done as part of the smoothing. This is an important preprocessing step when using CGM data, as using biased data could influence downstream processing. For instance in metabolism model parameter estimation, where bias correction and knowledge of the plasma-interstitial fluid time constant is needed to prevent CGM device-specific dynamics affecting the estimation of person-specific parameters. Our SMBG and FGM data does not allow us to conclude whether the biases we observed originate from the SMBG or the FGM measurements, but we assume the latter, since bias/calibration error is commonly found to be the largest error in CGM systems [32], [33], whereas SMBG measurement errors have been found to be uncorrelated in time [17]. It should be noted that glucose data sets with both CGM and frequent SMBG measurements as those analysed here, rarely occur outside research settings.

This work has considered glucose data sets, but the method should be applicable for other biomedical measurements that behave similarly, e.g. lactate. Some of the parameters (e.g. measurement and process noises) will need altering, but the general method should be applicable.

V. Conclusion

A Kalman smoother for automatic and objective preprocessing of glucose data has been presented, providing interpolation, outlier removal, replicate handling and uncertainty estimation in glucose data. Properties of the method have been discussed, and its performance on human glucose data sets containing SMBG and FGM measurements has been demonstrated. The method is recommended over some other methods that may be used for such tasks, e.g. linear or cubic spline interpolation, due to its noise suppression properties and its ability to estimate realistic variance (uncertainty) at each interpolated point. A Matlab implementation of the described method is publicly available [34].

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