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A Dual-Rate Kalman Filter for Continuous Glucose Monitoring

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***Abstract*— A dual-rate Kalman filter is developed for real-time continuous glucose monitoring. Frequent (5 minute) sampling of a noisy, continuous glucose sensor is used for estimation of glucose and its rate-of-change. Infrequent (8 hour intervals) reference glucose meter samples enable the sensor gain and its rate-of-change to be updated. The dual-rate Kalman filter formulation accounts for uncertainty in both the continuous glucose sensor and the reference glucose meter. The method is tested on simulated and experimental data, confirming its superiority to simple one-point calibration.**

I. Introduction

Diabetes mellitus is a metabolic disease characterized by high blood glucose levels (hyperglycemia) [1]. It is now well established that maintaining tight control on blood glucose is important [2], as hyperglycemia leads over time to complications such as heart disease, stroke, retinopathy, nephropathy and neuropathy. Intensive treatment requires careful monitoring of blood glucose, as it is associated with a higher incidence of hypoglycemia, also a dangerous condition [2].

In order to gain the full benefits, tight glucose control must be maintained for life. This requires constant vigilance, as insulin dose requirements change over time due to myriad factors, such as weight, stress levels and physical condition.

In the past few years continuous glucose sensors have been coming to market. The initial devices were blinded (*i.e.* glucose readings were not available until the device was downloaded to a computer), at which time retrospective fitting was done using blood glucose readings from a standard glucose meter [3]. In a recent study Garg *et al.* [4] have shown that un-blinded, real-time glucose readings from such a sensor can have a significant impact in improving glycemic control.

For practical reasons, these glucose sensors are subcutaneous, and measure glucose concentration in the tissue, not blood. Given that treatment decisions are made based on blood glucose, not tissue glucose, the sensor must provide a signal that is calibrated to glucose readings from fingerstick measurements.

This is not a trivial problem, as the relationship between tissue and blood glucose is dynamic. This is further compounded by the fact that the sensor signal degrades over time, due in part to depletion of the sensor's reagent, but more importantly due to the reaction of the immune system. Even though the new sensor systems have improved since the first generation appeared in the market, there is still plenty of room for improvement [5].

There are several methods for estimating blood glucose that have been proposed. These methods are often coupled with a commercially available sensor like the CGMS® System Gold™ of Medtronic MiniMed Inc. (Northridge, CA). The CGMS calibration method is retrospective, covering up to 72 hours of collected sensor data, and uses a least squares solution to estimate the sensor gain in a linear relationship [3]. A one-point calibration technique was developed by Choleau *et al.* [6], which uses the same linear relationship and assumes a known sensor intercept. Both of these methods are *a posteriori* in nature, requiring a lengthy window of past data to determine a future estimation equation. The Kalman filter technique used by Palerm *et al.* [7], Bequette [8], and Knobbe and Buckingham [9] is designed to handle the noise from sensor measurements and provide estimates of blood glucose in real time. It is also able to provide additional information, as done in [7] to provide an estimate of the rate of change of blood glucose. In this paper we present an implementation of the Kalman filter which we use to estimate the sensor gain as well as the blood glucose at the sensor's sampling rate, and use sporadic blood glucose fingerstick measurements to further improve performance.

II. Dual-Rate Kalman Filter Structure

Standard methods of estimating blood glucose levels, like the one-point [6] and retrospective [3] calibrations, are deterministic in nature, where noise in the sensor and reference blood glucose measurements can have significant effects on the blood glucose estimate. As the sensor degrades over time the sensor gain drifts, which also introduces error in the blood glucose estimate. These issues motivate the use of a stochastic estimation technique, which can handle noisy data, and which is capable of estimating other parameters (such as the changing sensor gain).

Underlying the Kalman filter structure is the discrete time, stochastic model

$$X_{k+1} = \Phi X_k + \Gamma U_k + \Gamma^w w_k \tag{1a}$$

$$Y_k = C X_k + \nu_k \tag{1b}$$

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where w_k and ν_k are, respectively, the input and measurement noise vectors (assumed to be uncorrelated Gaussian white noise). They have covariance matrices Q and R (respectively), which in practice are not known, so they become tuning parameters. If the measurements have a high degree of uncertainty and we want to trust the model more than the measurement, then R is weighted more relative to Q. Conversely, weighting Q high relative to R implies that the measurements are to be trusted more than the model predictions.

The predictor-corrector equations of the estimator are

$$\hat{X}_{k|k-1} = \Phi \hat{X}_{k-1|k-1} + \Gamma U_k \tag{2a}$$

$$\hat{X}_{k|k} = \hat{X}_{k|k-1} + L_k \left(Y_k - C\hat{X}_{k|k-1} \right) \tag{2b}$$

where $\hat{X}$ is the estimate of the states. The subscript notation $k|k-1$ indicates the estimate at time step k using measurements up to and including time step $k-1$. Equation (2a) is used to propagate the state estimate (using the model) from the most recent time step $k-1$ to the current time step k. Equation (2b) is then used to update the estimate, where L_k is the Kalman gain.

This Kalman filter gain is found by solving the equations

$$\begin{aligned} P_k = {} & \Phi P_{k-1} \Phi^T + \Gamma^w Q \Gamma^{wT} \\ & - \Phi P_{k-1} C^T \left(C P_{k-1} C^T + R \right)^{-1} C P_{k-1} \Phi^T \end{aligned} \tag{3a}$$

$$L_k = P_k C^T \left(C P_k C^T + R \right)^{-1} \tag{3b}$$

using an initial state covariance P_0.

One of the states to estimate is blood glucose, which is denoted as g_k, and which is expressed in terms of its rate of change

$$g_{k+1} = g_k + \Delta g_k \tag{4}$$

and this rate of change is modeled as a stochastic signal

$$\Delta g_{k+1} = \Delta g_k + w_{g,k} \tag{5}$$

whose change is due to process noise $w_{g,k}$.

The same is done for the sensor gain, which is the other state to estimate. In compact notation

$$\begin{bmatrix} a_{k+1} \\ \Delta a_{k+1} \end{bmatrix} = \begin{bmatrix} 1 & 1 \\ 0 & 1 \end{bmatrix} \begin{bmatrix} a_k \\ \Delta a_k \end{bmatrix} + \begin{bmatrix} 0 \\ 1 \end{bmatrix} w_{a,k} \tag{6}$$

and thus the full model is given by

$$\underbrace{\begin{bmatrix} g_{k+1} \\ \Delta g_{k+1} \\ a_{k+1} \\ \Delta a_{k+1} \end{bmatrix}}_{X_{k+1}} = \underbrace{\begin{bmatrix} 1 & 1 & 0 & 0 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 1 \\ 0 & 0 & 0 & 1 \end{bmatrix}}_{\Phi} \underbrace{\begin{bmatrix} g_k \\ \Delta g_k \\ a_k \\ \Delta a_k \end{bmatrix}}_{X_k} + \underbrace{\begin{bmatrix} 0 & 0 \\ 1 & 0 \\ 0 & 0 \\ 0 & 1 \end{bmatrix}}_{\Gamma^w} \underbrace{\begin{bmatrix} w_{g,k} \\ w_{a,k} \end{bmatrix}}_{w_k} \tag{7}$$

where the under-braces indicate the notation corresponding to the model in equation (1a). Note that in this case there are no inputs, thus $\Gamma = 0$.

The model has two measured outputs, sensor output and reference blood glucose (fingerstick) measurements, each on a different time scale. The sensor measurements are the fast time scale, with order of magnitude in minutes. The fingerstick measurements are more infrequent and on the slow time scale with order of magnitude in hours. The fast time scale output is given by

$$y_{s,k} = \underbrace{\begin{bmatrix} 0.5a_k & 0 & 0.5g_k & 0 \end{bmatrix}}_{C_{\text{fast}}} \underbrace{\begin{bmatrix} g_k \\ \Delta g_k \\ a_k \\ \Delta a_k \end{bmatrix}}_{X_k} + \nu_{s,k} \tag{8}$$

where the sensor output is split to be a function of both estimated states, as they must be observable in order for the Kalman filter to update both. For the slow time scale

$$\underbrace{\begin{bmatrix} y_{s,k} \\ y_{f,k} \end{bmatrix}}_{Y_k} = \underbrace{\begin{bmatrix} 0.5a_k & 0 & 0.5g_k & 0 \\ 1 & 0 & 0 & 0 \end{bmatrix}}_{C_{\text{slow}}} \underbrace{\begin{bmatrix} g_k \\ \Delta g_k \\ a_k \\ \Delta a_k \end{bmatrix}}_{X_k} + \underbrace{\begin{bmatrix} \nu_{s,k} \\ \nu_{f,k} \end{bmatrix}}_{\nu_k} \tag{9}$$

in which both the sensor output and the reference blood glucose measurement are available at this time. The noise terms $\nu_{s,k}$ and $\nu_{f,k}$ correspond, respectively, to the sensor and the reference blood glucose meter.

The resulting stochastic model, in compact notation, is then

$$\begin{aligned} X_{k+1} &= \Phi X_k + \Gamma^w w_k \\ y_{g,k} &= C_{\text{fast}} X_k + \nu_{s,k} \\ Y_k &= C_{\text{slow}} X_k + \nu_k \end{aligned} \tag{10}$$

It is important to note that while the Φ and Γ^w matrices are static, the presence of g_k and a_k as terms in the C_{fast} and C_{slow} matrices make them dynamic. This means that the underlying model itself is dynamic rather than static, and adapts to the sensor degradation over time. The common assumption that the Kalman gain is constant therefore does not hold, but an extended Kalman filter implementation is not necessary.

The dual-rate Kalman filter has two distinct updates which correspond to the fast and slow sampling rates. At the fast sample time, only the sensor measurement is used to update the estimated states. When the infrequent reference blood glucose measurements are available, both measured outputs are used to update the estimated states. The update at the fast sample time is given by the predictor/corrector equations in (11) and the update at the slow sample time is given by the corresponding predictor/corrector equations in (12).

$$\begin{aligned} \hat{X}_{k|k-1} &= \Phi \hat{X}_{k-1|k-1} \\ \hat{y}_{1,k|k-1} &= C_{\text{fast}} \hat{X}_{k|k-1} \\ \hat{X}_{k|k} &= \Phi \hat{X}_{k|k-1} + L_k^{\text{fast}} \left(y_{1,k} - \hat{y}_{1,k|k-1} \right) \end{aligned} \tag{11}$$

$$\begin{aligned} \hat{X}_{k|k-1} &= \Phi \hat{X}_{k-1|k-1} \\ \hat{Y}_{k|k-1} &= C_{\text{slow}} \hat{X}_{k|k-1} \\ \hat{X}_{k|k} &= \Phi \hat{X}_{k|k-1} + L_k^{\text{slow}} \left(Y_k - \hat{Y}_{k|k-1} \right) \end{aligned} \tag{12}$$

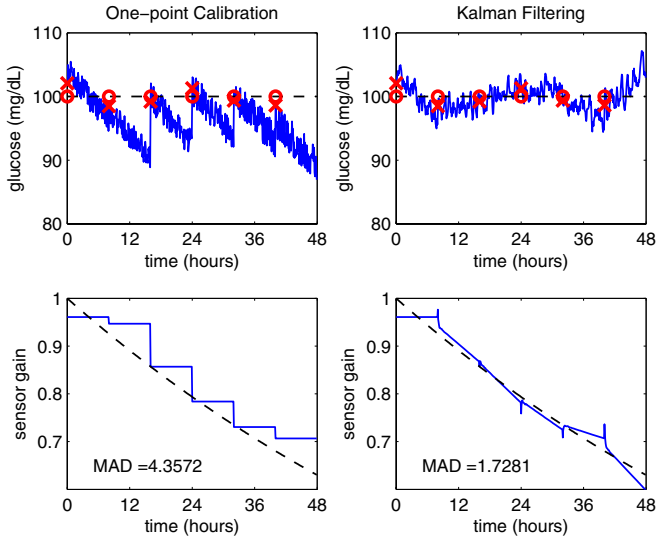

Fig. 1. Comparison of dual-rate Kalman filter (right) and one-point calibration (left) methods for estimating constant blood glucose with sensor degradation. Dashed line is the true underlying signal, solid line is the corresponding estimate, circles denote the actual blood glucose value, and the crosses the corresponding reference measurements.

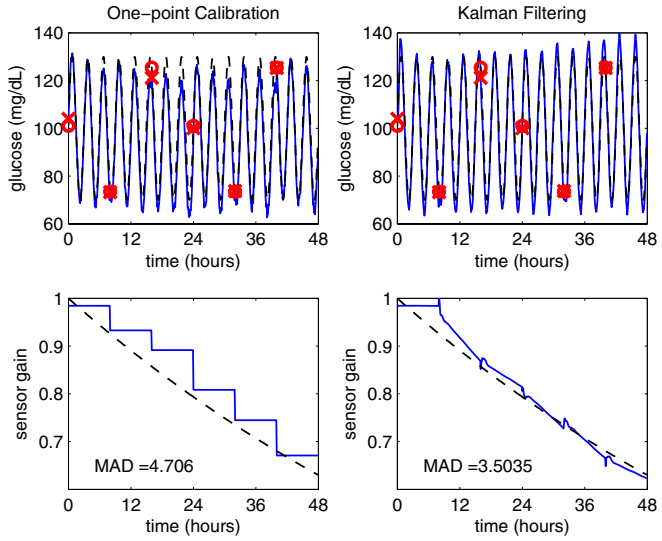

Fig. 2. Comparison of dual-rate Kalman filter (right) and one-point calibration (left) methods for estimating variable blood glucose with sensor degradation. Dashed line is the true underlying signal, solid line is the corresponding estimate, circles denote the actual blood glucose value, and the crosses the corresponding reference measurements.

It is important to note that the fast sample time can exhibit significantly different dynamic behavior than the slow sample time. This is incorporated in the dual-rate Kalman filter by having two dynamic Kalman gain terms, L_k^{fast} and L_k^{slow}. Each gain is allowed to vary dynamically with system behavior, and is updated at each respective sample time by solving the dynamic Riccati equation (3a).

III. Blood Glucose Estimation

The power of the dual-rate Kalman filter is in both its ability to handle measurement noise on multiple time scales and to operate in real time. This will be illustrated first by a comparison to the more traditional one-point calibration [6] method on a simulated glucose system, and then on experimental data.

The purpose of the comparison to a simulated ideal system is that the true underlying value of glucose is known, which provides a baseline for determining the efficacy of various estimation methods. The first ideal system is for a constant glucose value of 100 mg/dL and a sensor that degrades exponentially with a half life of 72 hours. The sensor was assumed to provide measurements with a 5 minute sample time and standard deviation of 2 mg/dL. Fingersticks were assumed to be taken every eight hours with a standard deviation of 5 mg/dL. Under these conditions, the one-point and dual-rate Kalman filter were both used to provide estimates of the blood glucose.

As figure 1 clearly shows, there is a significant difference in performance between the two estimation methods. The dual-rate Kalman filter is able to estimate the underlying blood glucose with much lower mean average deviation (MAD) than the one-point calibration technique. Updating the sensor gain and its rate of change by the dual-rate Kalman filter at both sample times allows for greater accuracy in tracking sensor degradation over the one-point calibration, which only updates sensor gain at fingerstick measurements.

The ideal simulated data used in figure 1 is based on constant blood glucose and sensor degradation. In reality, blood glucose levels will never remain constant for that period of time due to exercise, meals and natural fluctuations. To see how the dual-rate Kalman filter performs under variable blood glucose conditions with similar sensor degradation, sinusoidal blood glucose values were used in place of constant values.

Similar to the constant blood glucose results, figure 2 shows that there is a significant difference in performance between the two estimation methods. Using MAD values as a metric, the dual-rate Kalman filter is able to provide a better estimate of blood glucose levels than the one-point calibration technique.

Figure 3 shows the performance of the dual-rate Kalman filter using experimental data. The data comes from testing of an experimental subcutaneous glucose sensor on rats. The Q and R matrices for the dual-rate Kalman filter were tuned for this data set.

In figure 3, the performance of the dual-rate Kalman filter is compared against frequent blood glucose values and against the one-point calibration applied to the same data. The frequent blood glucose values have a low error margin, and thus are considered as the actual blood glucose levels. The "fingerstick" points are the times when the blood glucose values are used to update the slow sample time, adding noise (10% relative error, white Gaussian) to mimic a fingerstick in a subject with diabetes. A MAD value is calculated based on the reference blood glucose measurements; it shows that blood glucose was accurately estimated and that the dual-rate Kalman filter does a better job than the one-point calibration. It is also important to note that the dual-rate Kalman filter

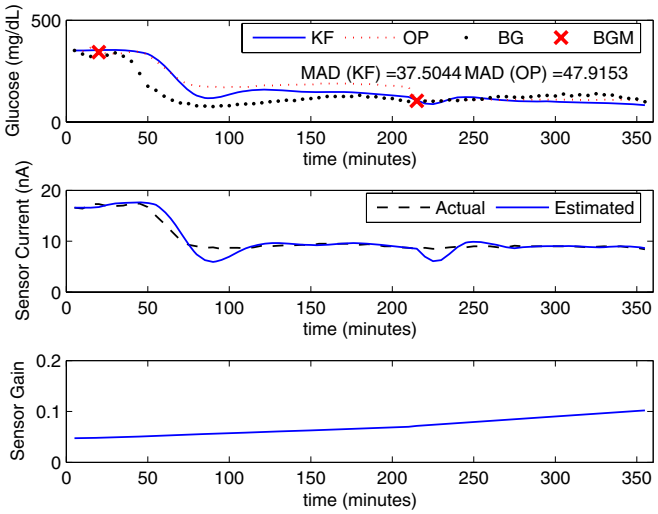

Fig. 3. Estimation of blood glucose and sensor signal using the dual-rate Kalman filter (KF) applied to experimental rat data (set 1); one-point calibration (OP) is shown for comparison.

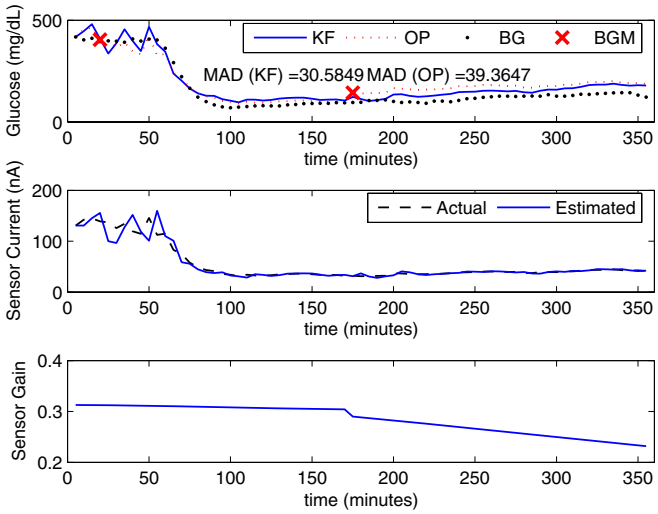

Fig. 4. Estimation of blood glucose and sensor signal using the dual-rate Kalman filter (KF) applied to experimental rat data (set 2); one-point calibration (OP) is shown for comparison.

was also able to accurately estimate the measured sensor current signal. In order to further test the dual-rate Kalman filter, it was applied to a second experimental data set, which was not considered in the tuning of the estimator. The results are shown in figure 4.

Similar to the first data set, a MAD value was calculated based on actual blood glucose values and compared against the one-point calibration technique. The dual-rate Kalman filter is again able to accurately estimate blood glucose levels and the measured sensor current signal, with two reference blood glucose values, used to update the slow sample time. Since the Q and R values used in this estimation were tuned for a separate and independent data set, this shows that the dual-rate Kalman filter also has a degree of robustness in tuning and performance.

IV. Conclusions

A dual-rate Kalman filter was developed for continuous glucose monitoring. The dual-rate Kalman filter takes advantage of information available at two time scales: frequent sensor measurements and infrequent fingerstick measurements. Using MAD as a performance metric, the dual-rate Kalman filter was shown to perform better than the a posteriori one-point calibration method on simulated data. Performance and robustness of the dual-rate Kalman filter was also shown compared to actual blood glucose values on two sets of experimental data.

It should be noted that, in this initial work, we have neglected the dynamic lag between the blood glucose and sensor current signals; compensation for this lag will most likely lead to better results, and is the topic of current work.

Acknowledgments

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