Optimal Estimation Applications to Continuous Glucose Monitoring

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***Abstract*—Type 1 diabetics must frequently monitor their blood glucose to avoid hypoglycemia and hyperglycemia. In this paper a Kalman Filter is developed to estimate blood glucose concentration from noisy continuous subcutaneous sensor signals. The Kalman Filter formulation leads to a natural blood glucose predictor that can be used to alarm patients to take corrective action to avoid hypoglycemia.**

I. Motivation and Background

Diabetes is a disease where the pancreas of an individual has impaired ability to produce insulin to regulate blood glucose. A type 1 diabetic has completely lost the ability to produce insulin and must receive daily injections, or continuous infusions, of insulin. Diabetics must closely monitor their blood glucose levels by pricking their fingers several times each day to obtain capillary blood glucose values from glucose test meters. This information, along with expected meal consumption, is used to adjust the amount of insulin delivered. A significant number of patients are on insulin pump therapy, where insulin is delivered in a nearly continuous fashion.

While intensive glucose management, based on obtaining 3-4 fingerstick glucose measurements a day, can result in reduced micro- and macro-vascular complications (with some increased hypoglycemia risk; DCCT, 1993), few diabetics monitor themselves at this rate. A number of continuous glucose monitoring devices are under development, based on subcutaneous or interstitial fluid sensing rather than direct blood glucose measurement. The availability of a continuous glucose signal has the potential to radically improve blood glucose maintenance; this is also necessary for the development of a closed-loop artificial pancreas (Parker et al., 2001; Belazzi et al., 2001).

Objectives of continuous glucose monitoring include the reduction of risk of hypoglycemia (low blood glucose) and the improvement of blood glucose management in individuals with diabetes. Challenges include compensation for the dynamic lag between the blood glucose and the sensed subcutaneous value, and the measurement noise associated with the subcutaneous sensor.

A review of blood and subcutaneous glucose dynamics is provided in section II, while sections III and IV develop techniques for blood glucose estimation and hypoglycemia detection.

II. Blood and Subcutaneous Glucose Dynamics

Current clinical practice is to make decisions on capillary blood glucose measurements, while most continuous monitors under development are based on subcutaneous sensing. A number of studies describe the blood-subcutaneous glucose dynamics as a first-order lag. Rebrin et al. (1999) use a compartmental approach to model glucose dynamics, as shown in Fig. 1.

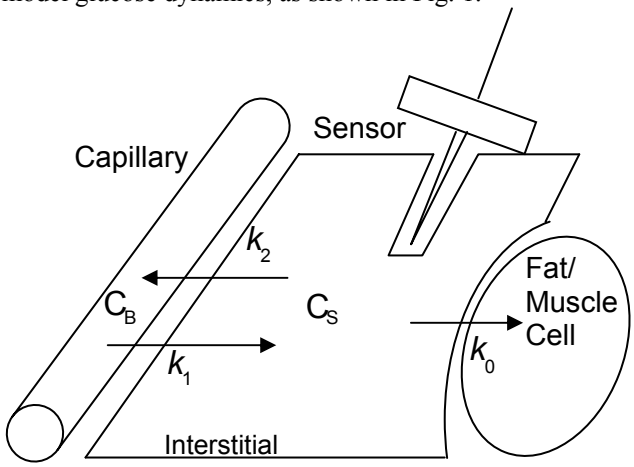

Fig. 1. Compartmental Representation of Capillary Blood and Subcutaneous (Interstitial) Glucose Dynamics (Rebrin et al., 1999).

The mathematical model is

$$\frac{dC_S}{dt} = -(k_{02} + k_{12})C_S + k_{21}\frac{V_1}{V_2}C_B \qquad (1)$$

where k_{02} represents a rate constant for the uptake of glucose in the subcutaneous tissues, k_{12} and k_{21} are rate constants for diffusion between the blood and subcutaneous compartments, V_1 and V_2 are the volumes of the blood and subcutaneous glucose compartments, respectively and C_B and C_S represent the blood and subcutaneous glucose concentrations. Rebrin et al. (1999) note that a diffusion coefficient can be defined as $D = k_{21}V_1 = k_{12}V_2$.

Schmidtke et al. (1998) consider a sensing volume (V), with glucose diffusion from the blood to the sensing

volume and uptake of glucose in the subcutaneous tissue. The relationship between blood (C_B) and subcutaneous glucose (C_S) concentration is

$$\frac{dC_S}{dt} = \frac{k_m A_m}{V}\left(C_B - C_S\right) - k_r C_S \tag{2}$$

where A_m is the mass transfer area and k_m is the mass transfer coefficient. They define the reciprocal of the mass transfer time constant as $\beta = k_m A_m / V$, and rewrite (2) as

$$\frac{dC_S}{dt} = -\left(k_r + \beta\right)C_S + \beta C_B \tag{3}$$

Schmidtke et al. found that β generally ranged between 0.04 and 0.11 min^{-1}, and $k_r = 0$ in their rat studies. Note that (1) and (3) are identical, with $\beta = k_{12}$, and $k_r = k_{02}$. Recall that the standard form for a first-order model is

$$\frac{dy}{dt} = ay + bu = -\frac{1}{\tau}y + \frac{k}{\tau}u \tag{4}$$

where u and y represent perturbations of the input and output from steady-state, and k and τ represent the gain and time constant. For (1) and (3), the gain and time constant are then

$$k = \frac{k_{12}}{k_{02} + k_{12}} = \frac{\beta}{\beta + k_r} \qquad \tau = \frac{1}{k_{02} + k_{12}} = \frac{1}{\beta + k_r} \tag{5}$$

Notice that if there is no uptake of glucose in the subcutaneous compartment, the gain, $k = 1$ for both (1) and (3). A given change in blood glucose then results in the same long-term change in subcutaneous glucose. The rat studies of Schmidtke assume $k = 1$, while Freeland and Bonnecaze (1999) show some simulation results for $k < 1$.

Schmidtke et al. indicated that τ ranged from 9 to 25 minutes in rats, while the dog studies of Rebrin et al. (1999) found that τ ranged from 5 to 12 minutes. Steil et al. (2003) studied humans and found $\tau = 3$ minutes.

Consider now the simple simulation model studied by Rebrin et al. (1999). The time constant is 12 minutes and the gain is 1. The blood glucose decreases from 200 to 100 mg/dl, with a first-order decay time constant of 75 minutes. The corresponding subcutaneous values, with measurement noise (standard deviation = 1 mg/dl), are shown in Fig. 2. This example will be used in the demonstration of estimation techniques in section III. While the measurement noise in Fig. 2 does not appear that dramatic, it does have a strong effect on the ability to estimate blood glucose from subcutaneous measurements. We should also note that the glucose monitoring literature sometimes erroneously refers to a "delay" between blood and subcutaneous glucose. The results in Fig. 2 are not characteristic of a time-delay, but rather a first-order "lag" (time constant).

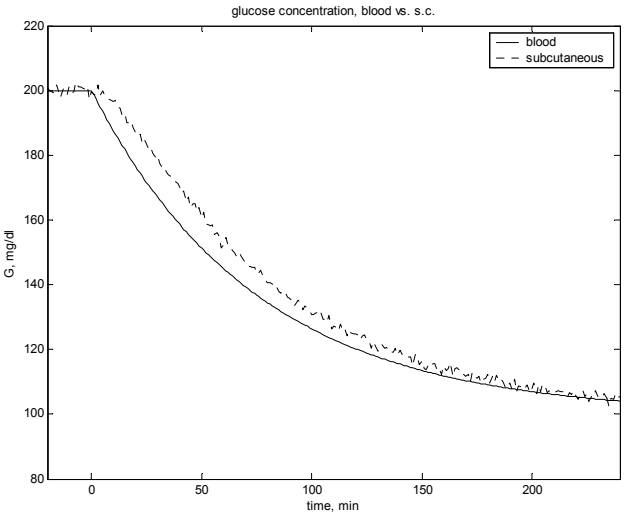

Fig. 2. Blood Glucose and Subcutaneous Glucose Responses. Subcutaneous Measurement Noise with a Standard Deviation of 1 mg/dl.

III. ESTIMATION

A. Intuitive Finite Differences Approach

Rebrin et al. (1999) develop an intuitive estimation approach for by rearranging (4) to solve for the blood glucose (u) from the subcutaneous glucose (y).

$$\hat{u} = \frac{\frac{dy}{dt} - ay}{b} \tag{6}$$

where ^ is used to indicate an estimated value. A finite-differences (FD) approximation for the derivative yields

$$\hat{u}_k = \frac{\frac{y_k - y_{k-1}}{\Delta t} - ay_k}{b} \tag{7}$$
$$\hat{u}_k = \left(\frac{1}{b\Delta t} - \frac{a}{b}\right)y_k + \left(-\frac{1}{b\Delta t}\right)y_{k-1}$$

Rebrin et al. (1999) note that this numerical derivative based approach is very sensitive to measurement noise, and also apply a three-point moving average filter on the measured output.

B. Kalman Filtering

Systems and control engineers, of course, immediately understand the limitations to the intuitive finite-differences approach presented above, and would generally apply optimal estimation-based techniques, such as the Kalman Filter. We use the following conceptual model

$$x_{k+1} = \Phi x_k + \Gamma u_k + \Gamma^w w_k \tag{8}$$
$$y_k = Cx_k + v_k$$

where w_k is an input noise vector (with covariance matrix Q), and v_k is a measurement noise vector (with covariance R). The noises are white "Gaussian" noise with zero mean. In practice, the noises are not known so Q and R are tuning parameters that affect the estimator performance. Weighting Q high relative to R indicates that the measured outputs are to be trusted more than the model predicted outputs. Conversely, weighting R high relative to Q indicates that any individual measurement has a high degree of uncertainty and the model predicted output should be trusted more than the measurement.

The maximum likelihood state estimates can be found recursively (Stengel, 1994), using the Kalman filter. The predictor-corrector equations are

$$\begin{aligned} \hat{x}_{k|k-1} &= \Phi \hat{x}_{k-1|k-1} + \Gamma u_k \\ \hat{x}_{k|k} &= \hat{x}_{k|k-1} + L_k\left(y_k - C\hat{x}_{k|k-1}\right) \end{aligned} \tag{9}$$

where $\hat{x}$ represents an estimate of the states and the notation for the subscripts $k|k\text{-}1$ means the estimate at step k is based on measurements up (and including) step $k\text{-}1$. Note that a model is used to propagate the state estimate from the previous time step ($k\text{-}1$) to the current time step (k). The measurement at the current time step is then used to update the state estimate, based on the Kalman Gain (L_k).

B.1. Step Disturbances

The formulation used here is slightly different than in (9) above; since the input (blood glucose) is unknown, it must be estimated. Defining the blood glucose (u) as a second state, we find (using matrix-vector notation) that (9) can be written in the form

$$\begin{aligned} \begin{bmatrix} x_{k+1} \\ u_{k+1} \end{bmatrix} &= \begin{bmatrix} \Phi & \Gamma \\ 0 & 1 \end{bmatrix}\begin{bmatrix} x_k \\ u_k \end{bmatrix} + \begin{bmatrix} 0 \\ 1 \end{bmatrix} w_k \\ y_k &= \begin{bmatrix} 1 & 0 \end{bmatrix}\begin{bmatrix} x_k \\ u_k \end{bmatrix} + v_k \end{aligned} \tag{10}$$

where it is assumed that the blood glucose changes randomly in step fashion. Notice that, in this case, the noise 'vectors' are scalars, so Q and R are both scalars and only their ratio is important. Using augmented state notation

$$x_k^a = \begin{bmatrix} x_k \\ u_k \end{bmatrix}, \Phi^a = \begin{bmatrix} \Phi & \Gamma \\ 0 & 1 \end{bmatrix}, \Gamma^{a,w} = \begin{bmatrix} 0 \\ 1 \end{bmatrix}, C^a = \begin{bmatrix} 1 & 0 \end{bmatrix} \tag{11}$$

The prediction-correction equations for this augmented state formulation are

$$\begin{aligned} \hat{x}^a_{k|k-1} &= \Phi^a \hat{x}^a_{k-1|k-1} \\ \hat{x}^a_{k|k} &= \hat{x}^a_{k|k-1} + L^a_k\left(y_k - C\hat{x}^a_{k|k-1}\right) \end{aligned} \tag{12}$$

For a time constant of 12 min. and a sample time of 1 min., the prediction and correction equations are (for $Q/R = 5$)

$$\begin{aligned} \begin{bmatrix} \hat{x}_{k|k-1} \\ \hat{u}_{k|k-1} \end{bmatrix} &= \begin{bmatrix} 0.92 & 0.08 \\ 0 & 1 \end{bmatrix}\begin{bmatrix} \hat{x}_{k-1|k-1} \\ \hat{u}_{k-1|k-1} \end{bmatrix} \\ \begin{bmatrix} \hat{x}_{k|k} \\ \hat{u}_{k|k} \end{bmatrix} &= \begin{bmatrix} \hat{x}_{k|k-1} \\ \hat{u}_{k|k-1} \end{bmatrix} + \begin{bmatrix} 0.52 \\ 1.71 \end{bmatrix}\left(y_k - \hat{x}_{k|k-1}\right) \end{aligned} \tag{13}$$

Here we have used a steady-state Kalman gain, L. The estimates using the two techniques are shown in Fig. 3. The KF-based estimates are clearly less noisy than the intuitive FD approach. The KF estimates exhibit a slight lag from the actual values, particularly immediately after the initial decrease in blood glucose.

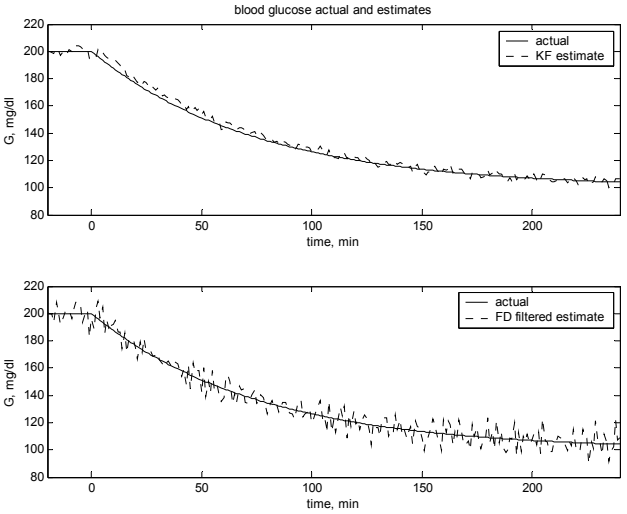

Fig. 3. Comparison of Kalman Filter-based Approach (top) with Finite-Differences Filtered Estimate (bottom).

B.2. Ramp Disturbance

A limit to the KF performance shown in Fig. 3 is the assumption of a random step change. Now, assume that the rate-of-change of blood glucose is constant. Define the change in blood glucose at step k as $d_k = u_k - u_{k-1}$

$$\begin{aligned} \begin{bmatrix} x_{k+1} \\ u_{k+1} \\ d_{k+1} \end{bmatrix} &= \begin{bmatrix} \Phi & \Gamma & 0 \\ 0 & 1 & 1 \\ 0 & 0 & 1 \end{bmatrix}\begin{bmatrix} x_k \\ u_k \\ d_k \end{bmatrix} + \begin{bmatrix} 0 \\ 0 \\ 1 \end{bmatrix} w_k \\ y_k &= \begin{bmatrix} 1 & 0 & 0 \end{bmatrix}\begin{bmatrix} x_k \\ u_k \\ d_k \end{bmatrix} + v_k \end{aligned} \tag{14}$$

At each time step the Kalman filter is estimating the subcutaneous and blood glucose, and the rate-of-change of blood-glucose, from noisy subcutaneous measurements. The results are shown in Fig. 4, where $Q/R = 0.05$ was used. Notice that there is less of a lag in the estimates based on a ramp change vs. step change. Estimating the rate-of-change of blood glucose will also quite naturally lead to a formulation for predicting when a hypoglycemic threshold might be reached, as shown in section IV.

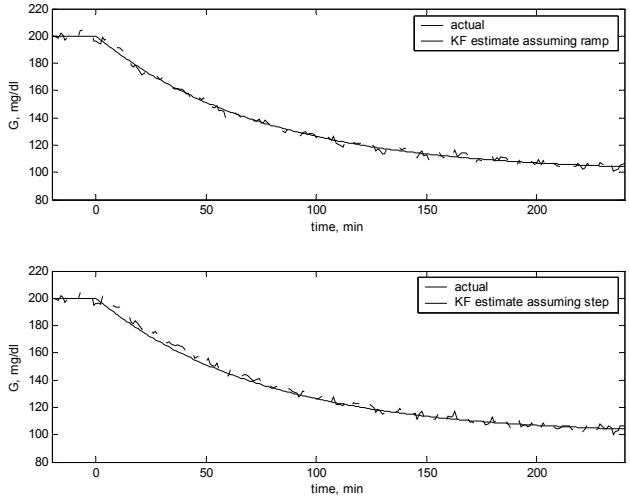

Fig. 4. Comparison of Kalman Filter-based Approach Assuming a Ramp Glucose Change Estimate (top) with a Step Change Estimate (bottom).

There has some debate about the relationship between blood and subcutaneous glucose, with some sources indicating that there is glucose uptake in the subcutaneous compartment and, therefore, a lower steady-state glucose concentration. This results in a gain < 1 for the first-order model. A Kalman Filter approach handles this case quite nicely, as shown in Fig. 5 (Q/R = 0.05).

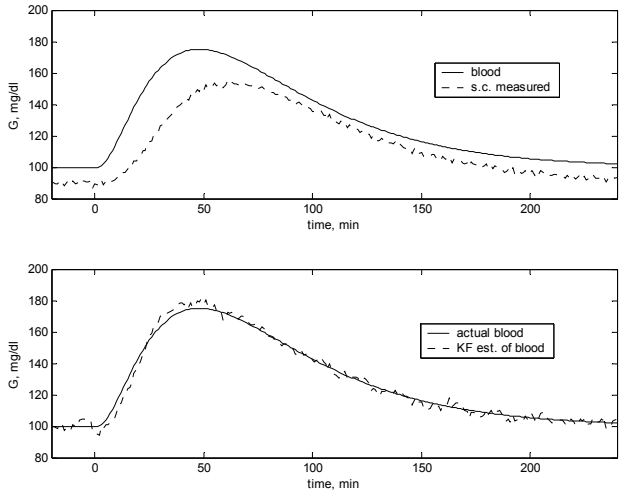

Fig. 5. Blood vs. Measured Subcutaneous (1 mg/dl std. dev. noise) Glucose (top); Blood Glucose vs. Estimate (bottom).

IV. Hypoglycemia Detection

One of the main objectives of continuous glucose monitoring is to reduce the risk of hypoglycemia. Choleau et al. (2002) estimate the rate of change of blood glucose concentration to predict when a hypoglycemic threshold (70 mg/dl) will be reached, and suggest that an alarm could be set to function when this prediction time drops to 20 min., allowing an individual to consume glucose to raise blood sugar. They use a linear regression algorithm that, by nature, adds a time delay to the prediction. We suggest a better approach based on optimal estimation theory.

In section III we showed how a Kalman Filter can be used to estimate the rate-of-change of blood glucose, even with significant measurement noise. This rate-of-change estimate can obviously be used to predict when a critical value of blood glucose will be reached. The prediction of blood glucose N steps into the future is

$$\hat{u}_{k+N|k} = \hat{u}_{k|k} + N \cdot d_k \tag{15}$$

defining u_{crit} as a critical blood glucose concentration (70 mg/dl in our studies), we can solve for the critical time, t_{crit}, by

$$t_{crit} = N\Delta t = \frac{u_{crit} - \hat{u}_{k|k}}{d_k} \cdot \Delta t \tag{16}$$

A characteristic decrease in blood glucose studied by Choleau et al. (2002) is shown in Fig. 6. Note the substantial lag between blood and subcutaneous glucose, with over a 10 min. difference in the times to reach the threshold of 70 mg/dl. Here again we assume measurement noise with a standard deviation of 1 mg/dl. Although there is a clear lag in the s.c. measurements, the blood glucose estimates track the actual values very well, as shown in Fig. 7. Also shown is t_{crit}, the predicted time before the hypoglycemic threshold of 70 mg/dl is reached. Note that the critical time of 20 min. occurs at approximately 18 min. The hypoglycemia prediction alarm could be set to warn the patient to consume glucose to avoid reaching a hypoglycemic state.

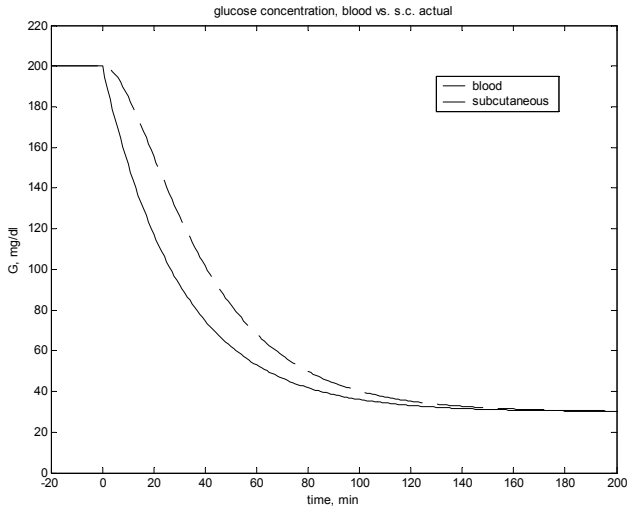

Fig. 6. Decrease in Blood and Subcutaneous (Noise-free) Gluocse Concentrations to Below the Hypoglycemic Threshold of 70 mg/dl.

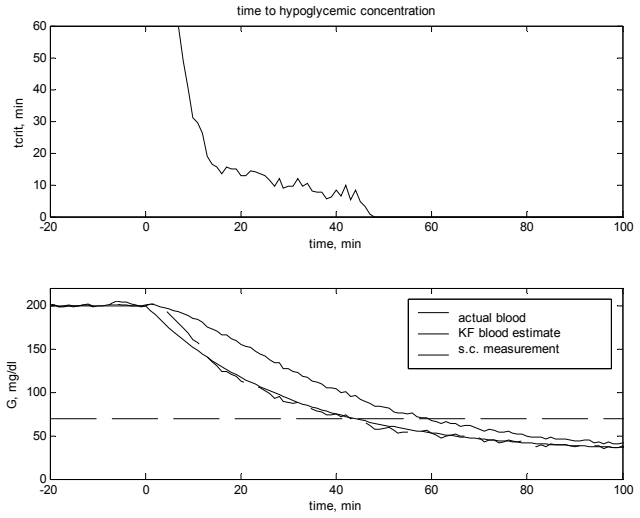

Fig. 7. Hypoglycemia Prediction. Top: Time predicted to reach the critical blood glucose concentration of 70 mg/dl. Bottom: Estimated and actual blood glucose concentrations, and subcutaneous measurement.

There are many important challenges in hypoglycemia detection and prediction, including the selection of thresholds and prediction horizons to provide reasonable rates of false positive alarms. In Palerm and Bequette (2004), a Kalman Filter is developed based solely on the subcutaneous glucose concentration. The rate-of-change (first derivative) and the second derivative of glucose are used as estimated variables, and used to predict future concentrations of subcutaneous glucose. The effect of measurement sampling frequency, hypoglycemic threshold, and prediction horizon on the sensitivity and specificity are studied. We propose a multi-tiered alarm system using different warning levels depending on the prediction horizon; i.e. predicting hypoglycemia over a shorter prediction horizon leads to a higher level warning than over a longer prediction horizon.

V. SUMMARY

A Kalman Filtering approach has been used to estimate blood glucose from noisy subcutaneous measurements. By appending a state related to the rate-of-change of blood glucose a natural formulation for predicting possible hypoglycemia arises. This predictor can then be used in a hypoglycemia awareness monitor, to provide diabetics with enough time to take corrective action to prevent hypoglycemia.

The estimation strategy presented can also be used in a model-based "artificial pancreas" to regulate blood glucose based on subcutaneous measurements and the adjustment of insulin infusion rates to maintain a desired blood glucose setpoint.

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