Interstitial fluid glucose time-lag correction for real-time continuous glucose monitoring

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A B S T R A C T

Time lag between subcutaneous interstitial fluid and plasma glucose decreases the accuracy of real-time continuous glucose monitors. However, inverse filters can be designed to correct time lag and attenuate noise enabling the blood–glucose profile to be reconstructed in real time from continuous measurements of the interstitial-fluid glucose. We designed and tested a Wiener filter using a set of 20 sensor–glucose tracings (~ 30 h each) with a 1-min sample interval. Delays of 10 ± 2 min (mean ± SD) were introduced into each signal with additive Gaussian white noise (SNR = 40 dB). Performance of the filter was compared to conventional causal and non-causal seventh-order finite-impulse response (FIR) filters. Time lags introduced an error of 5.3 ± 2.7%. The error increased in the presence of noise (to 5.7 ± 2.6%) and attempts to remove the noise with conventional low-pass filtering increased the error still further (to 7.0 ± 3.5%). In contrast, the Wiener filter decreased the error attributed to time delay by ~ 50% in the presence of noise (from 5.7% to 2.60 ± 1.2%) and by ~75% in the absence of noise (5.3% to 1.3 ± 1%). Introducing time-lag correction without increasing sensitivity to noise can increase CGM accuracy.

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1. Introduction

Diabetes can result in both acute and chronic complications – with the annual recorded number of sufferers increasing [1]. Several historic studies in Type 1 [2] and Type 2 Diabetes populations [3] have shown a reduction in morbidity and life-threatening disease through intensive management of glycaemia, either through multiple daily injections (MDI) or continuous subcutaneous insulin infusion (CSII). New innovative medical technologies are now available that have the potential to significantly reduce complications by increasing supervision of glucose levels through continuous glucose monitoring (CGM) [4]. For example, Jungheim et al. [5] demonstrated that by only monitoring 4 times daily with finger-stick sampling using customary blood glucose (BG) meter, a patient could miss up to 71% of hypoglycemic events, and when testing up to 7 times daily, a patient could miss 58% of events when compared to CGM.

The primary objective of this investigation is to improve the accuracy of CGM devices through improved calibration and front-end signal processing applied to the Guardian® RT system. The Guardian RT (Medtronic MiniMed, Northridge, CA) was the first real-time CGM device to be approved by the FDA in July 2005. The effectiveness of this monitor in lowering A1C was first demonstrated in the European GuardControl Trial [6], where the outcome showed a 0.6% improvement over the control group with the use of traditional self-monitoring of blood glucose (SMBG). Participants in the treatment group decreased their A1C levels by an average of 1%. More recently, the Juvenile Diabetes Research Foundation (JDRF) sponsored the largest CGM therapy study [7] to date that included the three major medical devices on the US market: FreeStyle Navigator® (Abbott Diabetes Care, Alameda, CA), Seven® (DexCom, San Diego, CA), and the Guardian RT. In this 322-subject study an A1C reduction of 0.5% was accomplished in the treatment group for the adult cohort in contrast to the control group with SMBG. The benefits of combined therapy with CGM and continuous subcutaneous insulin infusion (CSII) are more significant in comparison to mono-therapy with multiple daily insulin injections [8].

1.1. Physiologic time lag

In order to improve the accuracy of CGM devices we focus on the physiologic time differences. The aforementioned monitors estimate glucose from interstitial fluid (ISF) with minimally invasive electrochemical sensors inserted subcutaneously in the abdomen or upper arm [9], although non-invasive techniques by reverse iontophoresis transdermal glucose extraction exist [10]. As ISF glucose

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is the measurement signal for blood glucose inference, each glucose sample displayed in real time is lagging blood glucose by the summation of the time lag between ISF and plasma glucose, plus the inherent electrochemical sensor delay due to the reaction process [11], and any frontend signal processing delays required to produce smooth traces [12]. Rebrin and Steil [13] demonstrated through simulation and canine experiments that the time lag between ISF and plasma glucose can create errors of up to 6% – a number that will increase with additional delays introduced by signal processing. To improve the accuracy of CGM devices, the focus of this study is to mitigate time and denoise sensor signals to improve real-time accuracy of blood glucose estimation.

A range of methods have been considered to measure the aggregate time delay for CGM devices. Techniques range from the traditional correlation and regression estimation approaches used by Garg et al. [14], to the more novel Poincare plots approach by Kovatchev et al. [15]. Time lags associated with frontend digital filtering and the ISF-to-plasma glucose delay for marketed CGM devices has been reviewed in detail by the authors [11], including a detailed description of the Medtronic CGM frontend signal processing algorithms.

1.2. Time lag correction

Several investigations have attempted to mitigate physiological lag, both mechanically [16] and algorithmically [17]. Stout et al. [16] developed a novel approach to lag mitigation by modulating pressure to the measurement site in order to elevate blood perfusion, thereby decreasing the lag time for glucose to diffuse across the capillary barrier into the interstitial space. Although the authors showed a large decrease in delay following food intake by applying pressure modulation, the initial ISF lag times significantly exceeded the physiologic lag times reported in the literature from several human studies of subjects with and without diabetes [17–21]. It is possible that a significant portion of the reported lag may have been due to the measuring process as large transport times are intrinsic to micro-dialysis techniques used in this study. However, this technique produced a significant reduction in the overall time delay. In similar investigations time-lag has been reduced by identifying parameters in a model describing the diffusion process between the interstitial and blood–capillary compartments [17]. Gradient and delay parameters were estimated from the model based on plasma glucose and sensor-current samples from a subcutaneous enzymatic sensor. By rearranging a first order model, a plasma-glucose signal is calculated based on the measurement of sensor (ISF) glucose as input. While correcting delay, this approach generated noise in the resultant glucose signal, which was partially reduced by averaging a sensor-glucose derivative term.

An optimal estimation approach using a Kalman filter was adopted by Bequette [22] to estimate glucose from noisy signals. A conceptual discrete model was utilized consisting of a sensor glucose rate-of-change component as a state where the filter output is a prediction therefore reasonably unaffected by noise. The filter provided a degree of smoothing although the extent of time lag correction was not reported. The Kalman filter approach could potentially provide a de-noised signal with minimum delay, or incur no delay based on the filter’s predictive properties. Similarly, Facchini and et al. [23] accomplished time lag reduction with a population based model similar to the model previously described, as part of their extended Kalman filter. This particular algorithm performs delay correction within a calibration routine requiring only four reference values per day.

In the present study, the error increase attributed to time delay is investigated, and a Wiener filter is designed to perform inverse filtering to mitigate physiological time lag while at the same time reduce noise. The Wiener filter is compared to conventional filtering with simulated sensor tracings and calibrated with the Guardian RT routine. Filters are compared when applied to data collected from 10 patients in a clinical study undergoing closed-loop control [24].

2. Methods

2.1. Plasma ISF glucose dynamics

The two-compartment model [13] illustrated in Fig. 1 has been frequently used by a number of investigators to describe the dynamic relationship between ISF and plasma glucose [25–27]. This model is based on the assumption that the capillary space separating plasma and interstitial compartments creates a resistance to glucose diffusion into the interstitial space. Glucose is cleared from the ISF by a rate proportional to the concentration of glucose in that compartment. This mathematical relationship is described by the following mass balance equation:

\[
\frac{dV_2c_2}{dt} = -(k_{02} + k_{12})V_2c_2 + k_{21}V_1c_1
\]

(1)

with Laplace domain transfer function:

\[
\frac{C_2(s)}{C_1(s)} = \frac{K}{rs + 1}
\]

(2)

Here, the gain and time delay are defined by:

\[
K = \frac{k_{21}V_1V_2}{k_{02} + k_{12}}, \quad \tau = \frac{1}{k_{02} + k_{12}}.
\]

(3)

The plasma and ISF compartments have glucose concentrations \(C_1\) and \(C_2\), and corresponding volumes \(V_1\) and \(V_2\), respectively. The rate-of-glucose uptake from the subcutaneous tissue is determined by \(k_{02}\), and the fractional diffusion rates between the plasma and subcutaneous tissue are given by \(k_{12}\) and \(k_{21}\) (diffusion between compartments given as \(k_{12}V_2 = k_{21}V_1\) in units of mL/min, \(k_{12}\) and \(k_{21}\) are in units of fractional clearance or min\(^{-1}\)). The gradient between plasma and ISF glucose is defined as the steady-state ratio of \(C_2\) to \(C_1\) [17,28]. All rate parameters are assumed constant; therefore, the time lag between ISF and plasma-glucose concentration is also constant, as is the gradient. These parameters have been shown to be unchanged during rising and falling glucose levels and/or changing insulin concentrations [29]. Assuming sensor current to be proportional to glucose in the remote compartment \(((I(t)) = \alpha C_2(t))\), leads to:

\[
\frac{I(s)}{C_1(s)} = \frac{B}{rs + 1}, \quad B = \alpha K
\]

(4)

This equation can be transformed into the Z-domain using standard procedures [30]:

\[
\frac{I(z)}{C_1(z)} = \frac{Bz(1 - e^{-\tau/z})}{z - e^{-\tau/z}}
\]

(5)

![Fig. 1. Model of ISF plasma-glucose kinetics.](Image)
where $T$ is the sample time interval. During sensor calibration (one-point [31]), the sensor current is multiplied by a calibration factor ($CF = 1/B$) to produce a unity gain between sensor glucose ($SG$) and plasma glucose ($C_1$):

$$\frac{SG(z)}{C_1(z)} = \frac{z(1 - e^{-T/z})}{z - e^{-T}}$$

(6)

While calibration compensates for any gradient between $C_1$ and $C_2$, it does not remove the effect of delay. In addition, Eq. (4) does not include any component arising from noise in the sensor signal. However, compensation of a delayed signal in the presence of noise can be achieved using a Wiener filter approach. Derivation of such a filter proceeds in the time domain as:

$$SG(n) = a_1SG(n-1) + (1 - a_1)C_1(n) + \epsilon(n)$$

(7)

where $a_1 = e^{-T/T}$ and $\epsilon(n)$ is noise. A theoretical plasma-glucose-clamp response is illustrated in Fig. 2, with the resulting ISF glucose concentration superimposed with 0.8 gradient – which is typically observed in humans – and first-order time lag of 10 min. In this example, it takes approximately 50 min, which is equivalent to 5 time constants, for the transient response from ISF glucose concentration to completely equilibrate. As plasma glucose is estimated from a measurement of ISF glucose using an electrochemical sensor, a low current in the nA range is generated through the electrochemical reaction, which is considered to be proportional to ISF glucose. Traditionally, these sensors are calibrated via a capillary glucose measurement by fingerstick and BG monitor.

### 2.2. Plasma ISF channel equalization

Signals transmitted through various types of mediums can undergo distortion, where the received signal is degraded to some extent governed by the intrinsic properties of the medium. In order to recover the original signal from the received signal, a Wiener filter is often employed that provides an optimal trade-off between inverse filtering and noise reduction. When modeling the relationship between ISF and plasma glucose, the medium is the capillary space which separates the glucose measured in ISF and that measured in plasma. A set of filter coefficients can be used to describe this diffusion process.

The block diagram of Fig. 3 outlines this procedure, where the signal we wish to obtain is plasma glucose $s(n)$, the desired signal; and the signal we acquire through an electrochemical biosensor and CGM device is $x(n)$ – the received, or measurement signal. This measured signal $x(n)$ is distorted by the properties of the medium, i.e., the diffusion process previously described, which in signal-processing terms can be described by convolving the plasma-glucose signal $s(n)$ with an impulse response $h(n)$, which is the corrupting factor of the medium producing the degraded signal $y(n)$:

$$y(n) = h(n) \times s(n)$$

(8)

Here, the medium producing the signal is ISF, which is delayed relative to plasma glucose according to Eq. (4). Assuming a typical lag time of $\tau = 10$ min with a 1-min sample interval and unity gain, the transfer function will be of the form:

$$H(z) = \frac{zK}{z - e^{-T/T}} = \frac{0.0952}{1 - 0.9048z^{-1}}$$

(9)

The frequency and phase responses of this filter $H(z)$ are illustrated in Fig. 4, where a 10-min time delay can be identified at 0 Hz. Glucose changes at a very slow rate where signal information exists below the extremely low frequency (ELF) range. Steady-state glucose is measured at direct current and fast glucose digressions are typically observed at 2–3 cyc/h.

In practical applications, the ISF glucose signal is further degraded by additive white noise $\epsilon(n)$ to produce the resultant acquired signal $x(n)$:

$$x(n) = y(n) + \epsilon(n)$$

(10)

In an attempt to recover the desired signal $s(n)$, the measured signal $x(n)$, which includes both delay and noise, is processed by a $p$th order digital filter with filter coefficients $g(k)$:

$$s'(n) = \sum_{k=0}^{p} g(k)x(n-k) = g^T x$$

(11)

where $s'(n)$ is a Wiener filter output that estimates the original signal. To obtain the optimal filter coefficients $(g_{opt}(k), k = 0, \ldots, p)$, a calibrated electrochemical biosensor signal of 40 h duration was modified to create ideal and measurement signals. The sensor signal was sampled every minute and decimated to create the ideal
plasma-glucose signal with a sample time interval of 20 min, emulating the measurement resolution of laboratory blood analyzers. This ideal signal \(s(n)\) is illustrated by the red dashed trace of Fig. 5. The original sensor signal with a 1-min sampling interval was processed by diffusion filter \(H(z)\) with a first-order time lag of 10 min, producing the time delayed signal \(y(n)\) illustrated by the blue solid trace of Fig. 5.

To create a typical sensor glucose signal analogous to that acquired subcutaneously from ISF, white Gaussian noise was added to the glucose signal to an extent typical of electronic noise seen in the enzymatic sensor with signal-to-noise ratio (SNR) of 40 dB following hardware filtering common during the digitization process. The noise corrupted signal is shown as the solid trace \(x(n)\) in Fig. 6. Signals \(s(n)\) and \(x(n)\) are thus used to create the optimum set of Wiener filter coefficients.

### 2.3. Time-domain Wiener filter

An objective measure commonly used to determine an optimum set of Wiener filter coefficients is the mean square error (MSE) criterion. To solve the least-squares problem, we express, in matrix form, a set of \(N - 1\) sensor and BG values taken at 20-min intervals (columns), and \(p - 1\) sensor samples with 1-min interval (rows) for filter model order \(p\). The optimal set of filter coefficients, \(g_{\text{opt}}\), can be derived by standard least-squares analysis:

\[
g_{\text{opt}} = (Y^T Y)^{-1} Y^T s
\]

(12)
This approach uses a complete data-block formulation to derive the optimum set of coefficients. The frequency response of the resulting Wiener filter $G(x)$ is illustrated in Fig. 7 for the data shown in Fig. 6. Delay correction is evident from the frequency response occurring up to a frequency of $\sim 3$ cyc/h—a transition bandwidth is seen between $\sim 3$ and 5 cyc/h, and any signal above 5 cyc/h (noise) is attenuated. The time-lag correction properties can be seen from the phase response illustrated in the second trace of Fig. 7, where a lag correction of 10 min exists at DC.

In order to provide further noise reduction based on the Wiener filter attribute of optimal trade-off between delay correction and noise reduction, we bandlimited noise to above 6 cyc/h. Glucose typically changes at a slow rate, at least below 6 cyc/h. Therefore, by bandlimiting noise in the measurement signal to frequencies greater than this limit provides better stop-band attenuation beyond of the filter pass band.

A set of 20 sensor-signal profiles, sampled with 1-min time intervals, were each modified to incorporate lag times chosen from a random distribution with $10 \pm 2$ min (mean $\pm$ SD) with transfer function of equation [9]. White Gaussian noise was added to the sensor signals to produce SNRs of 40 dB. A set of Wiener filters were designed using the linear-time domain approach previously described. The time-delayed noise-corrupted signal $x(t_n)$, as well as the ideal signal $s(t_n)$ illustrated in Fig. 6, were applied to Eqs. (12) and (13), for model orders $N=4, \ldots, 64$, over a data segment of 4000 samples. The mean absolute relative difference (MARD) and SD were calculated for the 20 simulated signals for each model order. A filter order of $N = 30$ produced the optimum results ($2.6010 \pm 1.2657$). The performance of the Wiener filter for each model order is illustrated in Fig. 8. A filter model order of $N = 30$ will be used for the remainder of the tests presented in this paper.

3. Results

Each simulated sensor signal was processed with the Wiener filter and comparisons performed in the presence of absence of additive white noise. Further comparisons included the processing of each signal with a 7th-order low-pass finite-impulse response filter with a cut-off frequency of 3 cyc/h (previously used as part of a closed-loop glucose-control system [24]). The filter is applied with both causal and non-causal implementations and evaluated by means of point-by-point analysis. The MARDs are reported in Table 1.

The inclusion of a physiologic time lag introduced by the first order model creates a mean error of 5.3%, which increases by more than 0.4% when additive noise is applied with a SNR of 40 dB. The error incurred with the level of additive white noise just described can be considerably decreased by processing the signal retrospectively by the non-causal FIR filter, which removes filter time delay by forward and reverse filtering. This demonstrates that the error introduced by the FIR filter frequency response is minimal ($\sim 0.09\%$), i.e., while removing noise, a very minimal amount of signal information is distorted. The causal FIR filter produces an error of approximately 7% when utilized in real time. Therefore the filter group delay of 3.5-min introduced an additional error of approximately 1.6%. The Wiener filter produced the best results from the simulation dataset with errors of 1.34% with no additive noise and 2.6% with noise. Therefore, the Wiener filter yields a 4.4% improvement over conventional FIR filtering methods for the given dataset when a range of time lags is introduced. An example of the raw and Wiener filtered signals is illustrated in Fig. 9 for 11 h of duration, where the time-lag correction and noise-reduction properties of this filter are obvious.

A set of 10 sensor profiles of approximately 40 h of duration were each preprocessed by the same techniques with each approach applied to the Guardian RT calibration routine [32]. Each sensor profile was calibrated with 4 venous YSI data scans selected approximately 10 h apart. The MARD was measured by comparing the calibrated signals to venous YSI data samples acquired every 30 min, providing 592 evaluation points exclusive of calibration samples. The MARD and median error for each sensor and method is presented in Table 2.

**Table 1** Comparison of processing techniques for simulated signals.

<table>
<thead>
<tr>
<th>Method</th>
<th>Signal characteristics</th>
<th>MARD ± SD (%)</th>
<th>Median ± IR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No filtering</td>
<td>No additive noise</td>
<td>5.31 ± 2.68</td>
<td>5.11 ± 1.93</td>
</tr>
<tr>
<td>Non-causal FIR</td>
<td>40 dB SNR</td>
<td>5.74 ± 2.60</td>
<td>5.60 ± 2.30</td>
</tr>
<tr>
<td>Causal FIR</td>
<td>40 dB SNR</td>
<td>5.39 ± 2.72</td>
<td>5.18 ± 2.06</td>
</tr>
<tr>
<td>Wiener Filter</td>
<td>No additive noise</td>
<td>7.00 ± 3.48</td>
<td>6.72 ± 2.52</td>
</tr>
<tr>
<td>Wiener Filter</td>
<td>40 dB SNR</td>
<td>1.34 ± 0.97</td>
<td>1.18 ± 0.68</td>
</tr>
</tbody>
</table>

Fig. 6. Ideal and time delayed noise corrupted waveforms.
Fig. 7. The frequency and respective phase response of the Wiener filter with time-lag correction and noise reduction properties.

Fig. 8. Wiener filter percentage error calculated for increments in model order.

Fig. 9. Simulated raw and filtered signals plotted with the actual glucose profile.
Table 2
Comparative analysis for frequent sampled YSI dataset.

<table>
<thead>
<tr>
<th>Record</th>
<th>Wiener filter</th>
<th>FIR filter</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MARD ± SD (%)</td>
<td>Median ± IRQ(%)</td>
</tr>
<tr>
<td>1</td>
<td>15.03 ± 9.68</td>
<td>14.15 ± 15.76</td>
</tr>
<tr>
<td>2</td>
<td>13.22 ± 13.60</td>
<td>7.10 ± 10.20</td>
</tr>
<tr>
<td>3</td>
<td>13.64 ± 8.77</td>
<td>10.37 ± 12.96</td>
</tr>
<tr>
<td>4</td>
<td>13.32 ± 11.83</td>
<td>14.06 ± 16.50</td>
</tr>
<tr>
<td>5</td>
<td>18.36 ± 18.99</td>
<td>11.59 ± 19.96</td>
</tr>
<tr>
<td>7</td>
<td>8.42 ± 9.76</td>
<td>7.22 ± 12.07</td>
</tr>
<tr>
<td>8</td>
<td>13.47 ± 10.38</td>
<td>8.10 ± 11.51</td>
</tr>
<tr>
<td>9</td>
<td>8.54 ± 7.52</td>
<td>6.78 ± 6.94</td>
</tr>
<tr>
<td>10</td>
<td>6.62 ± 13.81</td>
<td>6.15 ± 9.64</td>
</tr>
<tr>
<td>Total</td>
<td>11.63 ± 10.89</td>
<td>9.39 ± 12.51</td>
</tr>
</tbody>
</table>

The Wiener filter produced aggregate mean and median errors of 11.63% and 9.39% which outperformed the standard low-pass filter approach in 8/10 records based on mean and 6/10 based on median error. The overall MARD is reduced by close to 2% and median error > 1% in comparison to the conventional approach of using the real-time FIR filter, yet achieving approximately the same degree of smoothing. The non-causal FIR filter produced a MARD of 12.11%, which is a 0.25% improvement over the raw, unprocessed signal. A 1.42% improvement is seen by removing the filter group delay and by filtering retrospectively. Although this is a real-time application, and filters cannot be applied retrospectively, this test illustrates the margin of error associated with increasing filter delays, which generally exceeds the error related to small levels of electronic noise.

An example record with over 40 h of duration is shown in Fig. 10. The time-lag-corrected sensor signal is shown in blue (dashed trace), which has been processed by the Wiener filter, and the second signal (solid trace) is processed by the low-pass FIR filter.

Four YSI points are used to calibrate the sensor signal in real time. Time-lag correction is evident where the Wiener filtered signal leads by approximately 10 min. The default low-alert hypoglycemia-warning threshold of 80 mg/dL would not have been triggered between 20–25 h and 35–40 h when the signal was preprocessed with the low-pass filter, while both events are captured when the signal is time-lag corrected prior to calibration. Thus, the hypoglycemic event between 20 and 25 h may have been averted when using the time-lag-corrected sensor signal, as the subject would have been alerted prior to hypoglycemia. Both Wiener and FIR filters have a comparable degree of smoothing.

4. Discussion

The CGM data presented in this study was very accurate as a result of a calibration process with multiple YSI reference measurements during a closed loop experiment. This is not possible with commercial devices outside of the clinic. This investigation specifically focused on preprocessing techniques and how they influence error, however, calibration routines can also further affect error. Commercially available CGM devices that measure ISF glucose are calibrated with capillary blood–glucose meters, which can decrease performance due meter accuracy, but to a greater extent the error can be increased by the lag time between plasma glucose and glucose measured in the interstitial space. This error can significantly increase during rapid glucose excursions, which are common following meals particularly with foods having fast absorption times.

The present study investigated the accuracy of preprocessing techniques applied to subcutaneous electrochemical sensor signals. Traditional approaches were compared to an optimal Wiener filter that attempts to correct for the physiological time lag between compartments with the additional benefit of noise reduction. A slight decrease in accuracy was demonstrated through simulation when increasing noise to give a SNR of 40 dB. When applying conventional FIR filters and retrospectively correcting for the filter group delay, the error decreased to approximately the same error with no additive noise. This result suggests that the filters’ frequency response, per se, produced very little distortion to the glucose signal. However, increasing the overall time delay by the additional group delay from the FIR filter increased the real-time error of the system by greater than 1.5%. The overall error improved when applying the Wiener filter to both simulated and in vivo signals, with the added benefit of producing smoothed sensor signals. A property of the Wiener filter allows for an optimally balanced trade-off between delay correction and noise reduction. When generating Wiener filter coefficients, increased noise reduction was achieved by adding noise only to undesired frequency bands, thereby producing further attenuation at these frequencies.

The Wiener filter stop band is similar to the FIR filter’s stop band and likely has similar filtering ability to other CGM filters such as Kalman [22] and median filter [33] approaches, perhaps with the exception of noise spikes and outliers where the a median filter may respond better in such circumstances. Infinite impulse response (IIR) filters can have sharper characteristics with the capability of a more intricate and rich frequency response. However, we explored the use of IIR Wiener based filtering for CGM and found FIR filters to be more practical, mostly for initialization purposes necessary with missing data. We were also able to reproduce the same filter response using either FIR or IIR approaches.

Although noise has been reduced and the results reflect more accurate readings, there exists some distortion in the signal. The origin of this slight deformation in the in vivo tracings is not known and could be a symptom of using white noise that has been bandlimited, as opposed to white Gaussian noise. In the results presented, certain records improved significantly with lag correction, while performance decreased in a small number of sensors. It is expected that performance would improve in all records should the Wiener filter be applied to perfect sensors. Glucose sensors are imperfect; therefore, time lag correction in an under-reading sensor, perhaps due to sensor drift since calibration, could produce a higher error. Such sources of error are not accounted for in this preprocessing algorithm. This was seen in simulated tests, including records with outlier time lags exceedingly different from the mean lag time of 10 min.

Filters which do not incorporate an accurate model of the underlying physiological process either by data dependence, as in the case of the adaptive Kalman filter, or by application of a kinetic model of the underlying physiology are unable to correctly reduce physiological time lag. We chose a Wiener filter due to its time-lag correction properties with optimal noise reduction. A time lag of 10 min was used as it is equal to the pairing time delay used in the calibration algorithms. Therefore, not only is physiologic time lag
5. Conclusion

The variation in physiological time delay that would exist in a large patient population is yet to be determined, as are the metabolic factors that may cause intra- and inter-subject variability. To better understand the rate of plasma-glucose diffusion to the interstitial space in a broader population of subjects with varying characteristics, studies would need to implement reasonably high blood–glucose sampling rates to compare with instantaneous ISF glucose measurements. A first-order time lag is a reasonable model to explain the diffusion process. In this investigation, a time-lag correction of 10 min produced optimal results when applied to signals collected from 10 patients during a closed-loop study. A performance improvement of approximately 2% is achieved by mitigating time lag with error reduction evident in most sensors. However, it is expected that with a greater variance in time lag this error will increase, but to an extent that is less than conventional filtering. In addition to improving performance the Wiener filter enables patients to monitor their blood-glucose levels in real time. Real-time readings from current CGM devices lag blood glucose by the physiological delay between glucose measured in plasma and glucose measured in ISF plus FIR filter group delays discussed in this paper. Therefore, the Wiener filter provides faster event detection and increased patient safety.

References


Fig. 10. Resultant signals following processing with FIR and Wiener filters plotted with frequently sampled (2 min) venous blood glucose measurements.


