Detection of a Meal Using Continuous Glucose Monitoring (CGM): Implications for an Artificial β-cell

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ABSTRACT

Objective: The purpose of this study was to introduce a novel meal detection algorithm (MDA) to be used as part of an artificial β-cell that utilizes continuous glucose monitoring (CGM).

Research Design And Methods: We developed our MDA on a data set of 26 meal events using records from nineteen children 1 to 6 year old who used the Medtronic Minimed CGMS Gold®. We then applied this algorithm to CGM records from a DirecNet pilot study of the FreeStyle Navigator® (Abbott Diabetes Care). During a research center admission, breakfast insulin was withheld for 1 hour and discrete glucose levels were obtained every 10 minutes following the meal.

Results: Based on the Navigator readings, the MDA detected a meal at a mean time of 30 minutes from the onset of eating, at which time the mean serum glucose was 21 mg/dL above baseline (range 2 to 36 mg/dL), and more than 90% of meals were detected before the glucose had risen 40 mg/dL from baseline.

Conclusion: The meal detection algorithm will enable automated insulin dosing in response to meals, facilitating the development of an artificial pancreas.
The development of an artificial β-cell is a challenging task, which has drawn together different disciplines within engineering, science, and medicine for the past 30 years (1). In the most likely scenario, the subject is connected to both a continuous subcutaneous insulin infusion (CSII) system and a continuous glucose monitor (CGM). The loop is “closed” inside a computer / personal data manager (PDM) by software that regulates the glucose level by changing the insulin infusion rate of the pump. The success of such an artificial β-cell is dependent on the following: (a) predictive mathematical models of patients that can mimic glucose absorption secretion and insulin action (for example the pharmacokinetic / pharmacodynamic models in (2; 3); (b) reliable and accurate sensors that transmit real-time glucose measurements; (c) automated insulin pumps that can be software controlled; (d) a controller (algorithm) that can regulate glucose by changing the infusion rate based on sensor glucose measurements. A variety of controllers can be found in the literature that are capable of regulating glucose. Several are based on mathematical models and designed as PID or MPC (4-7), others are based on fuzzy logic (8). However, as was noted by Hovorka (9), a number of challenges remain to be solved before the artificial β-cell is realized: one of the critical challenges is the regulation of glucose levels following a meal (10). The meal challenge can be met, in principle, by three different approaches; the first one is the feed forward control approach where the user of the artificial β-cell will inform the controller that a meal is occurring (or is about to occur) by clicking a button, thus initiating an insulin bolus. The second way is to rely strictly on feedback control, whereby the algorithm will respond only after a sufficiently large rise in glucose has occurred. This particular strategy has proven difficult in practice owing to the tradeoff between the need to respond quickly due to the delay in insulin absorption and the need to have a conservative scheme that does not deliver an overdose of insulin. The third approach is discrete meal detection; this will trigger an insulin bolus as part of an algorithm using continuous feedback from a CGM. One can envision that the first and third schemes could be combined, such that the discrete meal detection algorithm is a failsafe mode for a patient-initiated feedforward scheme. This manuscript details a reliable meal detection suite of solutions that was validated with historical data CGM data and can be implemented as part of an artificial β-cell controller.

RESEARCH DESIGN AND METHODS
Detection of meal related glucose excursions were initially assessed using the data from 26 meal events when subjects were wearing a Med Minimed Gold CGM® and had marked the onset of a meal. These records were obtained from nineteen children ages 1 to 7 (mean age 5 years) who were participating in an outpatient study (11). The data presented here was taken from a DirecNet pilot study of the FreeStyle Navigator® real-time continuous subcutaneous glucose sensor (12), which is currently an investigational device. This study of thirty children with type 1 diabetes treated with insulin infusion pump therapy included a clinical research center (CRC) admission. All subjects over age 8 signed an assent, and all parents signed a consent approved by the institutional review board at each participating DirecNet center. Twenty-one of the subjects had their breakfast dose of insulin withheld for 1 hour in order to induce a rapid increase in blood glucose levels. Some children did not
undergo this test because of their weight and the amount of previous blood sampling. For those participating in the meal challenge, blood samples were obtained every 10 minutes for 1 hour following completion of breakfast. All subjects had been admitted to the CRC the previous day, and all were wearing a FreeStyle Navigator® continuous glucose sensor which was recording interstitial blood glucose levels every minute. The average age of the subjects was 11 ± 4 years (range 4 to 17) and 40% were female. Mean duration of diabetes was 6 ± 3 years. Mean A1c was 7.1 ± 0.6%.

**Rate Of Change Calculation.** The glucose rate of change (ROC) is estimated by two different methods; both are based on real-time glucose measurements sampled at one minute intervals. The first approach is a calculation of glucose rate of change using a three point (current and two previous samples) backward difference (13):

\[
\frac{dG_i}{dt} = \frac{3G_i - 4G_{i-1} + G_{i-2}}{2\Delta t}
\]  

(1)

where \( G \) is the glucose measurement, \( t \) is time, \( \Delta t \) is the time difference between two samples intervals and the subscript \( i, i-1, i-2 \) are the current and two previous samples respectively.

The second approach is based on optimal estimation theory, using a Kalman filter (14; 15), an established method that have been used as part of different algorithms in the context of glucose management such as: hypoglycemic / hyperglycemic prediction (16; 17), improved glucose monitoring (18; 19) and feedback control (7). This method assumes that the glucose sensor signal varies primarily through two contributions: (a) real changes to the underlying glucose value, \( (g_k) \), and (b) measurement noise, \( v_k \). Hence the glucose can be expressed in terms of its rate of change (\( d_k \)):

\[
g_{k+1} = g_k + d_k
\]  

(2)

such that the value at time \( k+1 \) is the value at the previous time step \( k \) plus the rate of change. Similarly the rate of change can be expressed in terms of the rate in the previous time step plus the acceleration or the rate of change of the rate of change (\( f_k \)):

\[
d_{k+1} = d_k + f_k
\]  

(3)

where the acceleration term is a stochastic signal that is changed by a random amount that can be interpreted as process noise (\( w_k \)):

\[
f_{k+1} = f_k + w_k
\]  

(4)

where \( w_k \) has a mean value of 0 and a covariance of Q. The glucose measurement is corrupted by random measurement noise with zero mean and covariance R

\[
G_k = g_k + v_k
\]  

(5)

Equations 2-5 can be written in matrix-vector form as:

\[
\begin{bmatrix}
g \\
d \\
f_{k+1}
\end{bmatrix} =
\begin{bmatrix}
1 & 1 & 0 \\
0 & 1 & 1 \\
0 & 0 & 1
\end{bmatrix}
\begin{bmatrix}
g \\
d \\
f_k
\end{bmatrix} +
\begin{bmatrix}
0 \\
0 \\
1
\end{bmatrix} w_k
\]  

(6)

\[
G_k =
\begin{bmatrix}
1 & 0 & 0
\end{bmatrix}
\begin{bmatrix}
g \\
d \\
f_k
\end{bmatrix} + v_k
\]  

(7)

Equations 6 and 7 are commonly called discrete state space models, and the following notation is commonly used in the systems and control literature:
\[ x_{k+1} = \Phi x_k + \Gamma^w w_k \]
\[ y_k = C x_k + v_k \]  

(8)

where \( x \) is a vector of states and \( y \) is the measured output. In this application, the matrices and vectors have the following values:

\[
\Phi = \begin{bmatrix} 1 & 1 & 0 \\ 0 & 1 & 1 \\ 0 & 0 & 1 \end{bmatrix}, \quad \Gamma^w = \begin{bmatrix} 0 \\ 0 \end{bmatrix}, \quad C = \begin{bmatrix} 1 \\ 0 \\ 0 \end{bmatrix}, \quad x = \begin{bmatrix} g \\ d \\ f \end{bmatrix}, \quad y = G \]

(9)

Since both the measurement and process noise are considered stochastic processes, their unknown covariances can be used as the tuning parameters. Hence, the tuning parameter used is related to the ratio of the expected process to sensor noise variance (\( Q/R = 5 \times 10^{-6} \)). The states are estimated using a predictor corrector equation of the form:

\[
\hat{x}_{k|k-1} = \Phi \hat{x}_{k-1|k-1} \]

(10)

\[
\hat{x}_{k|k} = \hat{x}_{k|k-1} + L_k \left( y_k - C \hat{x}_{k|k-1} \right) \]

(11)

where \( \hat{x} \) is the estimation of the states; the subscript \( k|k-1 \) indicates the estimation at time step \( k \) using the previous value; the process model is transformed using the standard notation (\( \Phi \), \( \Gamma \) and \( C \)); and \( L \) is the Kalman Gain. More details on the use of Kalman estimation in general and in the context of diabetes can be found in (14-16).

The best estimate, at the current sample time, of the states (glucose, rate-of-change of glucose, and rate-of-change of the rate-of-change of glucose) is

\[
\begin{bmatrix} \hat{g} \\ \hat{d} \\ \hat{f} \end{bmatrix}_{k|k} = \hat{x}_{k|k} \]

(12)

In the discussion that follows, we will simply refer to these estimated states as \( G \), \( G' \), and \( G'' \); that is, at any sample time

\[
\begin{bmatrix} G \\ G' \\ G'' \end{bmatrix} = \begin{bmatrix} \hat{g} \\ \hat{d} \\ \hat{f} \end{bmatrix}_{k|k} \]

(13)

**Detection Algorithm.** The proposed algorithm for meal detection is divided into five stages as illustrated in the flowsheet in Figure 1, and detailed below (20):

(a) The first stage is data acquisition, where the last five minute reading from the CGM is conveyed to the algorithm. This data is processed in parallel by a rate of change component and a Kalman filter estimation algorithm.

(b) In the second stage, the rate of change estimation can be broken down into: (1) backward difference rate of change calculation (BD) based on the raw data; (2) BD estimation based on the glucose estimation from the Kalman filter (BD and Kalman); (3) Kalman filter estimation of glucose (\( G \)) and the rate of change (\( G' \) (Kalman)) and (4) the Kalman estimate of the rate of change of the rate of change (\( G'' \)). This yields four separate inferences of the actual rate of change.

(c) The estimated rate of change is compared to a threshold value that corresponds to a meal-related rise in glucose and is screened using multiple heuristics to minimize false positive detections. We have identified four design variables that can be tuned according to individual subjects: (a) a glucose ROC threshold (1.8-3 mg/dL-min); (b) a maximum glucose ROC (2-5 mg/dL-min), (c) a glucose threshold (150-220 mg/dL) and (d) an acceleration threshold (0.4 - 0.8 mg/dL-min). A secondary screening condition
Meal Detection Algorithm For Artificial β-cell

to minimize noise artifacts is the requirement that the glucose values will increase monotonically. As a safety interlock measure, a meal declaration will not be issued if such a declaration was issued 15-20 minutes earlier, and a night safety condition prevents any meal announcement during the night. This condition can be adjusted for the lifestyle of an individual patient. These safety layers can minimize false detections and lead to a more reliable automated system.

(d) A voting algorithm is implemented, to minimize the risk of an unnecessary insulin bolus. A meal flag will be sent only if two out of three methods, or three out of four methods consistently detect a meal in the same five minute time window.

(e) Finally, the controller will receive a meal flag and/or the algorithm will reset for the next data point.

Statistics. Kruskal-Wallis one way analysis of variance on ranks was used to assess significance of the mean time from onset of the meal and the mean increase in glucose values from baseline when a meal was recognized by the four proposed algorithms (SigmaStat, SPSS Inc.).

RESULTS

The results from the seventeen subjects admitted to the CRC as part of the DirecNet study (21) are summarized in Table 1. Subjects consumed an average of 56 grams of carbohydrate for breakfast (range 22 to 105 grams). The table details, for each meal detection method, the time it took to detect the meal (∆T) and how much the glucose had increased from baseline when a meal was detected (∆G). An example of meal detection is provided in Figure 2. In this example, the four different methods succeeded in detecting the breakfast meal in less than 20 minutes from the onset of that meal, and there was less than a 22 mg/dL increase of the glucose from the preprandial value. In this figure a false-positive meal detection is seen where G” detected a meal before breakfast. The voting scheme, however, would have prevented this from being a false-positive event. In Table 1 the meal detection time for each of the voting schemes (three-out-of-four and two-out-of-three) is denoted for each of the 17 breakfast meals. Using a voting scheme of three-out-of-four, the overall mean detection time from all data sets was 32 minutes with a mean increase in the serum glucose of 21 ± 9 mg/dL from the onset of eating. Using a voting scheme of two-out-of-three, the mean detection time was 30 minutes with a mean increase in the serum glucose of 15 ± 10 mg/dL from the onset of eating.

A summary of the results showing how well the “challenge” breakfast meal was detected in all seventeen cases by the four different methods is presented in Table 1 and Figure 3. The average detection time from the onset of the “challenge” meal was 29, 35, 31 and 30 minutes respectively (Table 1), for the BD, Kalman, BD + Kalman and G” algorithms, and the average detection time from the end of the meal was 11, 18, 13 and 12 minutes, respectively. The glucose only increased by a mean of 2 mg/dL from the onset of the meal to the completion of the meal, despite a mean of 17 minutes to complete a meal. One can infer from Figure 3 that the Kalman estimation is more conservative than the other methods. This is a result of how the Kalman filter was tuned and, in our opinion, is beneficial in improving the robustness of the voting scheme and providing an additional layer of safety. A second critical factor is the increase in glucose by the time of meal detection. This information is presented in Figure 3, which shows that 100%, 94%,
100% and 94% of meals were detected before a 40 mg/dL increase in the glucose using the BD, Kalman, BD + Kalman and G” methods respectively, and 94%, 59%, 100% and 94% of meals were detected before a 30 mg/dL increase in the glucose using the respective methods.

CONCLUSIONS
Meal detection is a critical and enabling component of a control algorithm for an artificial β-cell. Independent of whether one employs a PID, MPC or another control algorithm, the ability to have an automated meal announcement, that does not require patient input, is an important factor. In reviewing the literature, we were unable to find another paper in the medical or engineering literature which specifically addressed the issue of meal detection by using a continuous glucose sensor. We therefore evaluated meal detection algorithms using a FreeStyle Navigator® that measures interstitial glucose. In addition, the insulin bolus for breakfast was delayed by one hour, allowing us to evaluate the rate of change (ROC) of glucose values following a meal without the confounding effects of an insulin bolus at the time of the meal. The content of the breakfast meals was decided by the study subject and these meals varied significantly in their composition and grams of carbohydrate, as would occur in their home environment. These conditions therefore mimic the expected conditions for recognizing a meal in a fully closed-loop artificial β-cell.

A critical element of a meal detection algorithm is minimization of the time between the actual meal and the detection flag. This depends on a variety of factors including the meal composition, how long it took to consume the meal, insulin on board, and the amount of noise in the data. Using our algorithm that employed a voting scheme of two-out-of-three methods to detect a meal, the mean detection time from the onset of the meal was 30 minutes and the mean increase in the serum glucose was only 15 mg/dL. It is our impression that this algorithm combined with a rapid acting insulin will provide the means to prevent significant postprandial hyper and hypoglycemia in a closed-loop system, but this remains to be tested.

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REFERENCES

TABLE 1. Results summary showing the meal times with the glucose value at the time of the meal with the four detection methods, detection time and glucose level in deviation form from the onset of the meal value.

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<th>( \Delta T^* ) (min)</th>
<th>( \Delta G^* ) (mg/dL)</th>
<th>( \Delta T^* ) (min)</th>
<th>( \Delta G^* ) (mg/dL)</th>
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\(^{(*)}\) Detection time from the onset of the meal; \(^{(**)}\) Difference between the glucose level on detection minus the glucose level at onset of the meal; \(^{(**)}\) Trigger of meal flag by the voting scheme algorithm of three-out-of-four, mean detection time of 32 minutes from the onset of eating, at which time the mean serum glucose was 21±9 mg/dL above baseline; \(^{(**)}\) Trigger of meal flag from the voting scheme algorithm of two-out-of-three (BD, BD+Kalman, G”) mean detection time of 30 minutes from the onset of eating, at which time the mean serum glucose was 15±10 mg/dL above baseline. **The mean blood glucose using the Kalman algorithm was significantly higher compared to the other methods (p < 0.001)
**FIGURE LEGENDS**

**Figure 1.** Algorithm for implementing a safe meal detection that will minimize the false positive detection (invoking an unnecessary insulin bolus). The different detection methods are: backward difference (BD), Kalman Filter estimation (Kalman), combination of BD and Kalman (BD+Kalman) and second derivative of glucose (G’’). The voting algorithm consists of either a two-out-of-three (BD, BD+Kalman, G’’), or three-out-of-four (BD, Kalman, BD+Kalman, G’’) scheme, respectively.

**Figure 2.** A zoomed view of a sample of one data record of the challenged meal of a subject with meal detection using the different methods; presenting real time measurements that have been collected using CGMS as black line, Freestyle finger sticks data as dots and annotation of event as text with rectangles including meal (start and/or stop) and snacks annotated as diamonds. The meal was detected anywhere from 9 to 19 min from the onset, and the glucose level had increased by 3 - 22 mg/dL (20).

**Figure 3.** Increment of glucose values from onset of the challenged meal until detection of meal for the four different detection methods.
FIGURE 1

- CGMS Data from the last 5 min
- Wait for next data point
- ROC Calculation on raw data
- Kalman estimation, G, G', G''
- ROC Calculation Based on Kalman Glucose estimation
- Detection Algorithm (BD, Kalman, BD + Kalman and G'')
- Voting system on meal event (3/4) or (2/3)
- Yes: Meal Flag to the controller
- No: Continue waiting for next data point
FIGURE 2

![Graph showing glucose levels over time with flagged meal markers.]

Legend:
- Glucose
- FreeStyle
- Meal Markers
- Events
- BD
- Kalman
- BD + Kalman
- G^*
FIGURE 3

Increment Of Glucose From Onset Of The Meal To Detection Time (mg/dL)