Real-Time Hypoglycemia Prediction Suite Using Continuous Glucose Monitoring

A safety net for the artificial pancreas

EYAL DASSAU, PHD
FRASER CAMERON, MS
HYUNJIN LEE, PHD
B. WAYNE BEQUETTE, PHD
HOWARD ZISSEr, MD

LOIS JOVANOVIC, MD
H. PETER CHASE, MD
DARRELL M. WILSON, MD
BRUCE A. BUCKINGHAM, MD
FRANCIS J. DOYLE III, PHD

OBJECTIVE — The purpose of this study was to develop an advanced algorithm that detects pending hypoglycemia and then suspends basal insulin delivery. This approach can provide a solution to the problem of nocturnal hypoglycemia, a major concern of patients with diabetes.

RESEARCH DESIGN AND METHODS — This real-time hypoglycemia prediction algorithm (HPA) combines five individual algorithms, all based on continuous glucose monitoring 1-min data. A predictive alarm is issued by a voting algorithm when a hypoglycemic event is predicted to occur in the next 35 min. The HPA system was developed using data derived from 21 Navigator studies that assessed Navigator function over 24 h in children with type 1 diabetes. We confirmed the function of the HPA using a separate dataset from 22 admissions of type 1 diabetic subjects. During these admissions, hypoglycemia was induced by gradual increases in the basal insulin infusion rate up to 180% from the subject’s own baseline infusion rate.

RESULTS — Using a prediction horizon of 35 min, a glucose threshold of 80 mg/dl, and a voting threshold of three of five algorithms to predict hypoglycemia (defined as a FreeStyle plasma glucose readings <60 mg/dl), the HPA predicted 91% of the hypoglycemic events. When four of five algorithms were required to be positive, then 82% of the events were predicted.

CONCLUSIONS — The HPA will enable automated insulin-pump suspension in response to a pending event that has been detected prior to severe immediate complications.

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The Diabetes Control and Complications Trial (DCCT) proved that glucose control in the closer-to-normal range (tight glycemic control) reduced the likelihood of eye, kidney, nerve, and cardiovascular complications of diabetes (1,2). Unfortunately, the DCCT also showed that the incidence of severe hypoglycemia was three times higher in the intensively treated group compared with the standard treatment group (1). In the DCCT, 55% of the severe lows occurred during sleep hours (1). Further, in the adolescent portion of the DCCT, the risk for severe hypoglycemia was even greater, with one episode every 1.17 years (85.7 per 100 patient-years) (2). One report in children found 75% of severe lows to occur during the nighttime hours (3). The high frequency and duration of nocturnal hypoglycemia has been confirmed in clinical research center (CRC) studies, in which frequent laboratory reference glucose values were obtained. For example, in a DirecNet study of exercise-induced nocturnal hypoglycemia, children who did not exercise had a 28% incidence of nocturnal hypoglycemia (glucose <60 mg/dl), and those who exercised had a 48% incidence of nocturnal hypoglycemia (4). In a recent study (5) of bedtime snacks and nocturnal hypoglycemia, on nights when adult subjects did not have a snack, 57% became hypoglycemic (<70 mg/dl), with an average duration of hypoglycemia of over 2.5 h. In this study, the duration of hypoglycemia was as long as 8.75 h.

Real-time continuous glucose monitoring (CGM) is becoming available with the Food and Drug Administration (FDA) approval of the MiniMed Guardian, the DexCom STS, and the Abbott Navigator. One of the major perceived benefits of real-time glucose monitoring is the ability of these devices to have alarms for hypoglycemia. For a real-time alarm to be effective, it must awaken a sleeping subject. The first FDA-approved real-time glucose monitor was the GlucoWatchTM. To determine whether the alarm function on the GlucoWatch was effective in awakening children while they were sleeping, an infrared camera was used to videotape them throughout the night in the CRCs. During this admission, reference glucose values were obtained every half hour to document hypoglycemia. In this study, 71% of youths wearing the watch did not respond to nighttime alarms (6), placing these patients at a risk for nocturnal hypoglycemia despite wearing a real-time continuous glucose sensor. One possible correction of this problem would be to have the sensor send a signal to the pump so that it will stop infusing insulin when pending or real hypoglycemia has been reached and the patient has not responded to alarms. This is the primary focus of the hypoglycemia prediction algorithm.

Previous studies (7–9) have shown that when insulin infusion is stopped for 2 h or when an infusion set is disconnected for up to 30 min (7), there is essentially no risk of the patient developing significant ketones or acidosis. Three previous studies (8–10) have demonstrated that turning off an insulin pump for 2 h...
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did not result in diabetic ketoacidosis (DKA). In all three studies, blood β-hydroxybutyrate concentrations were determined using both a meter (Precision Xtra™) and the hospital laboratory. In two of the studies (9,10), the continuous subcutaneous insulin infusion pumps were purposely turned off for periods of 4 and 5 h, with a gradual increase in β-hydroxybutyrate concentrations after 2 h to the upper normal range. No cases of DKA occurred in these studies.

**RESEARCH DESIGN AND METHODS** — The hypoglycemia prediction algorithm (HPA) was developed using data derived from 21 Navigator studies, which assessed Navigator function over 24 h in children with type 1 diabetes, aged 3–18 years, conducted in clinical research centers (CRCs) (11). Then the HPA functionality was confirmed using a separate dataset from 22 CRC admissions of type 1 diabetic subjects with a mean age of 20 years (range 6–38). In this study, hypoglycemia was induced by gradual increases in the basal insulin infusion rate by a mean of 180%, 18 of 22 subjects (82%) reached a glucose value of ≤60 mg/dl (12,13). Promising results were reported by Buckingham et al. (12), where when two different algorithms were used 60% of the pending hypoglycemic events were predicted and prevented.

CGM data were introduced to the HPA as if it were a real-time measurement; the different algorithms analyzed the data and an alarm was produced if a quorum was reached by the voting algorithm. Three hypoglycemia thresholds of 70, 80, and 90 mg/dl were evaluated, each with three different prediction horizons (V) of 35, 45, and 55 min and with three voting thresholds of 3, 4, and 5.

**Hypoglycemia Prediction Algorithm**
The core of the HPA is a set of individual alarms that are combined through a voting system into one combined alarm. With each new CGM datum, each individual alarm will run independently and will indicate hypoglycemia or euglycemia. Then, if the number of individual alarms that have gone off in the last 10 min is above a preset voting threshold (V), the voting alarm will trigger. A low voting threshold will generate more alarms, giving more warning but less accuracy. Finally, the combined alarm will trigger if either the voting alarm or the threshold alarm goes off. Figure 1 shows the flow of the combined hypoglycemic detection algorithm (14). Glucose predictions and analysis from CGM data can be performed in more than one way by applying different mathematical methods such as optimal estimation techniques (15,16), time series (17), and other methods. The HPA system consists of five prediction algorithms:

1. **Linear projection:** This alarm uses a 15-min linear extrapolation and uncertainty threshold based on the SD of the glucose measurements in the previous 15 min.
2. **Kalman filtering:** A Kalman filter is used to estimate glucose and its rate of change, which are then used to make predictions about future glucose levels. The filter is tuned to trade off the probability that a measured glucose change is real versus the result of sensor noise. The approach is presented in more detail in simulation studies by Palerm et al. (16) and applied to clinical hypoglycemic clamp data in Palerm and Bequette (18) and as part of a meal detection algorithm in Dassau et al. (19).
3. **Hybrid infinite impulse response filter:** The infinite impulse response filter takes advantage of a linear discrete-time signal-processing method (20) that generates output predictions using previous output (measured glucose concentration) without input (insulin infusion). Predicted outputs are recursively applied to the filter coefficients for a prediction horizon. The filter coefficients are updated when prediction and parameter errors are larger than user-specified bounds. The hybrid filter prediction with a factor (α) between fixed and adaptive filter coefficients is considered for safe and accurate glucose predictions. It is flexible to tune the filter performance by adjusting the data window length (WL), prediction horizon (p), and error criteria (εi and εs).
4. **Statistical prediction:** Multiple empirical, statistical models are used to estimate future blood glucose values and their error bounds. From these, a probability of hypoglycemia is generated and thresholded to produce an alarm. The statistical prediction algorithm is divided into three compo-
ents: 1) calibration, which converts raw CGM and capillary blood glucose measurements into a physiologically consistent, accurate blood glucose history; 2) prediction, which uses training data and the recent calibrated blood glucose history to generate predictions and associated accuracy estimates; and 3) hypoglycemic alarming, which transforms the predictions and accuracy estimates into a probability of the patient becoming hypoglycemic, which is then thresholded into a binary alarm (12, 21).

5. Numerical logical algorithm: Numerical logical algorithm feeds a three-point calculated rate of change using backward difference approximation and the current glucose value into logical expressions to detect impending hypoglycemia. The logical expressions verify that the rate of change is both negative and within an acceptable range as well as that the CGM glucose values are within predefined boundaries and that a pending hypoglycemic event is predicted within the threshold time window. Numerical logical algorithm provides insensitivity to sensor signal dropouts and easy tuning.

Voting system
The voting system, as described in Fig. 1, polls each algorithm to determine whether it should alarm. If the number of algorithms that predict hypoglycemia is above the voting threshold (V) more than twice in a time window of 10 min (first crossing will prime the alarm and the second will fire the alarm) or the sensor blood glucose is below the hypoglycemic threshold, then the alarm sounds. Therefore, an alarm sounds if one of the following is true:

- The number of individual alarms meets or exceeds the voting threshold;
- The sensor interstitial glucose value is below the hypoglycemic threshold.

RESULTS — The five hypoglycemic prediction alarms were run for all proposed parameter combinations on 18 sets of data from 18 admissions. It should be noted that the reported results are based solely on the predictive part of the method.

As can be seen from Fig. 2, hypoglycemia was reached at around noon (defined as glucose ≤ 70 mg/dl). This event has been predicted by the different algorithms 55, 45, and 35 min ahead of the event, and an alarm could have been issued at this time depending on the quorum threshold (e.g., 55-min warning time if two different algorithms were to issue a positive vote twice in a 10 min window). If the number of positive alarms required was three or four, a warning time would have been 40 and 35 min, respectively, sufficient time for a suspension of the pump to have prevented the event.

Table 1 shows the results from running the individual and combined algorithms against the historical pump shut-off data. The numbered columns (e.g., 1, 2, 3, 4, and 5) indicate the voting threshold for the case. The data also show that the prediction rate declines as the voting threshold increases. This can be seen in the range of prediction times obtained by varying the settings of the tuning param-
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Table 1—HPA ability to predict hypoglycemia events based on historical datasets with different voting thresholds

| Prediction horizon (min) | Alarm threshold (mg/dl) | Percent predicted hypoglycemic events for the given alarm scenario |
|-------------------------|-------------------------|---------------------------------------------------------------|
|                         | 1 | 2 | 3 | 4 | 5 | KF | SP | HIIR | NLA | LP |
| 35                      | 70 | 91 | 64 | 55 | 36 | 18 | 82 | 55 | 45 | 91 | 55 |
| 45                      | 70 | 100 | 82 | 73 | 64 | 36 | 100 | 64 | 64 | 91 | 73 |
| 55                      | 70 | 100 | 100 | 100 | 82 | 36 | 100 | 100 | 82 | 91 | 100 |
| 35                      | 80 | 100 | 100 | 91 | 82 | 45 | 100 | 100 | 82 | 91 | 82 |
| 45                      | 80 | 100 | 100 | 100 | 91 | 64 | 100 | 100 | 91 | 91 | 91 |
| 55                      | 80 | 100 | 100 | 100 | 100 | 82 | 100 | 100 | 100 | 91 | 100 |
| 35                      | 90 | 100 | 100 | 82 | 73 | 55 | 100 | 100 | 91 | 64 | 73 |
| 45                      | 90 | 100 | 100 | 82 | 82 | 55 | 100 | 100 | 100 | 64 | 73 |
| 55                      | 90 | 100 | 100 | 82 | 82 | 55 | 100 | 100 | 100 | 64 | 73 |

LP, linear prediction algorithm; KF, Kalman filter algorithm; HIIR, hybrid impulse response filter; NLA, numerical logical algorithm; SP, statistical prediction algorithm.

The effectiveness is an important factor since too many false alarms are a detriment to safety systems will result in disconnecting of the system by the user, rendering the system useless. HPA tuning knobs (prediction horizon, alarm threshold, and voting threshold, as seen in Table 1) allows the algorithm to be adjusted to meet the subject preferences as far as defining the hypoglycemia threshold, time to alarm prior to the event, and aggressiveness of the algorithm. These settings could vary between day and night and be tuned to meet individual insulin sensitivity, allowing the user to enhance specificity that would prevent false alarms resulting in pump suspension, where during the day a more aggressive tuning can be set that can alert the user to take corrective action prior to the need to suspend the pump. The use of a CGM in clinical decision making is the first step toward the artificial pancreas. The prevention of nocturnal hypoglycemia based on glucose predictions as well as missed-meal alarms will reduce glucose variability and clinical complications resulting from extreme blood glucose concentrations. CGM technology, together with telemedicine applications such as E911 (22), can provide remote glucose monitoring and triangulation as well as pump suspension. This technology will help in improving the well-being of people with diabetes and peace of mind to families of children with diabetes.

When a safety algorithm is suggested, the false-positive rate is equally as important as the true-positive rate. The evaluation of the true positive has been addressed based on retrospective analysis of clinical data. The specificity of the algorithm was further evaluated.

Figure 3—HPA evaluation using the UVa/Padova Metabolic Simulator following a clinical scenario in which an erroneous basal delivery, twice the usual one, was set by the user. As can be seen in the plot, without the use of HPA the subject experienced severe hypoglycemia (red dashed line) and with the algorithm this event was prevented (blue line) by suspending the basal rate for 90 min and restoring the correct basal (green dotted line). The black dashed-dotted line denotes the hypoglycemia threshold as defined by blood glucose. A high-quality digital representation of this figure is available in the online issue.
prospectively using the UVa/Padova
FDA-accepted (23) Metabolic Simulator
and is currently under clinical evaluation
that will be reported in a subsequent pub-
lication. The frequency of false-positive
alarms of the HPA has been assessed by
running the simulator under standard
conditions with a meal at 5:00 P.M., start-
ing the hypoglycemia prediction algo-
rithms at 9:00 P.M. and running it until
7:00 A.M. the following morning before a
breakfast meal. Furthermore, the HPA
was evaluated overnight using twice the
usual basal insulin in order to induce hy-
poglycemia. The prospective analysis
of the algorithm with tuning of 80 mg/dl, 45
min, and two for hypoglycemia thresh-
old, prediction horizon and voting
threshold, respectively, is provided be-
low. This simulation supported the clini-
cal results with only four in silico subjects
crossing the 60 mg/dl blood glucose
threshold out of 100 in silico adult sub-
jects, where the glucose nadir is margin-
ally <60 mg/dl. As can be seen from Fig.
3, the HPA predicted a pending hypogly-
cemic event when glucose concentration
was ~104 mg/dl and suspended the
pump for 90 min. This result in prevent-
on of the event where, in successive sim-
ulation without the use of the algorithm,
the glucose dropped to extremely low val-
ues. The false-positive rate of the algo-
rithm with the same tuning was 9% based
on a population of 100 different in silico
subjects and noisy sensor. However, only
three out of the nine cases where a false
alarm was issued resulted in a glucose el-
evation of >20 mg/dl from the baseline
that resulted in hyperglycemic event. It
should be noted that this needs to be fur-
ther evaluated by extensive clinical trials
to better assess the algorithm.

The use of a sophisticated voting al-
gorithm allows an extra degree of safety
prior to issuing an alarm. In addition, vot-
ing enables the use of five different indi-
vidual algorithms to predict pending
hypoglycemia and not to rely on one al-
gorithm that may or may not be the most
suitable to address the variability among
type 1 diabetic subjects. Furthermore,
the use of a suite of algorithms allows a more
robust system that can cope with glucose
variability and the different glucose drop
patterns that may affect rate of change and
the ability to detect a pending event by a
single algorithm.

**CONCLUSIONS** — The use of the
HPA would allow for triggering of a warn-
ing alarm and/or suspension of an insulin
pump, which should decrease the risk of
severe hypoglycemia. Based on clinical
evaluation, insulin delivery will most
likely need to be suspended 30–50 min
before a projected hypoglycemic event in
order to prevent most hypoglycemic events
(12). On one hand, longer predic-
tion time may provide greater ability to
prevent hypoglycemia events; on the
other hand, it may be impractical to sus-
pend a pump too far from an event that
may not happen due to human factors
(e.g., a planned meal). The Hypoglycemia
Prediction Algorithm (HPA) tuning al-
lows flexibility in the aggressiveness of
the alarm and can be set to meet user prefer-
ces. Furthermore, this technology can
be easily implemented in current CGM
systems and as a safety net to further arti-
ficial pancreas development.

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