Technology

Addressing the time-lag between blood glucose levels and continuous glucose monitor readings

Peter Hammond, Consultant in General Medicine, Harrogate

One of the potential limitations of continuous glucose monitoring (CGM) is the time-lag between the blood and interstitial glucose levels.

The data obtained from the CGM sensor is processed and adjusted according to capillary blood glucose readings so that it approximates the blood glucose level. However, the time-lag between the actual blood glucose level and the comparable interstitial glucose level reading obtained from the sensor means that any sensor reading must be interpreted with caution. Crucially, the sensor reading must be confirmed with a capillary blood glucose measurement before action is taken on it, in terms of insulin adjustment or carbohydrate intake. Not only does this time-lag have implications for today's user of real-time CGM, but it complicates the development of a closed-loop insulin delivery system.

Any algorithm designed to adjust insulin delivery according to a sensor glucose reading has to make allowances for this time-lag, and additionally the delay between subcutaneous insulin delivery and peripheral insulin action, which is probably around 30 minutes.

The time-lag has two components: the time it takes for blood glucose to equilibrate with the interstitial fluid such that glucose levels are comparable, and instrumental delay in processing the raw data from the sensor in the interstitial fluid. Previous studies have reported lag-times ranging from 15 to 30 minutes, while some authorities have suggested it may be even greater at times of rapid blood glucose change – perhaps up to 45 minutes.

In defining the time-lag, various assumptions must be made, and in particular, how to model the blood glucose and CGM data to allow the time-lag to be calculated. If the mathematical model distorts the raw data too much then the estimate of time-lag is likely to be erroneous.

Kovatchev et al (summarised alongside) describe a new mathematical model for comparing the data obtained from CGM using the FreeStyle Navigator (Abbott, Maidenhead) and laboratory blood glucose estimation. They used a Poincaré-type plot and matched CGM and blood glucose values using various different time differences looking for the plot with the least spread of values. Graphically, this was seen at 15 minutes time difference, and using further analyses based on a logarithmic transformation to generate a normal distribution, calculated the time-lag as 12.5 minutes.

The authors demonstrated that there was no difference in time-lag when the sensor was worn on the arm or abdomen. They also showed that, as expected, at times of rapid decrease in blood glucose (at least 1 mg/dL/min) the time-lag was greater, at an average of 16.8 minutes, but when there was a similarly rapid increase in blood glucose the time-lag was reduced, at 9.9 minutes.

One advantage of this mathematical model is that it uses raw CGM data, so while the time-lag may have a component related to the instrument, the processing of the sensor data is discounted as an issue. The conclusion that the time-lag ranges from 9.9 to 16.8 minutes provides a degree of reassurance that, while time-lag must be considered when interpreting CGM output, it is neither sufficiently great, nor does it vary so much between times of rapid increase and decrease in blood glucose levels to cast doubt on its value as a tool for adjusting insulin therapy.

DIABETES TECHNOLOGY & THERAPEUTICS

Better representation of the CGM time-lag

Readability	✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓✓

1 Subcutaneous continuous glucose monitors measure interstitial glucose levels and require calibration with blood glucose readings.

2 Interstitial glucose levels lag behind blood glucose levels because of the time taken for glucose to diffuse into the interstitial space. This study investigated a new algorithm to calculate and compensate for this time-lag in continuous glucose monitoring (CGM).

3 The algorithm was tested by retrospective analysis of data from 56 CGM time series collected by the FreeStyle Navigator, from 28 people with type 1 diabetes.

4 Each participant wore two sensors (on arm and abdomen) and blood glucose reference values were collected with a YSI analyser every 15 minutes.

5 The average time-lag observed between reference blood glucose values and CGM was 12.5 minutes. The time-lag was longer when blood glucose was falling (16.8 minutes), compared with steady or rising blood glucose (11.7 and 9.9 minutes, respectively; $P<0.005$), when stratified by blood glucose rate of change.

6 There was no significant difference between time-lags at the two sensor locations: 12.4 minutes on the arm, 12.6 minutes on the abdomen.

7 Substantial blood-to-sensor time delays were observed. Analysing blood glucose to CGM co-dynamics in this way resulted in convenient visualisation and numerical estimation of the time-lag.

Kovatchev B, Shields D, Breton M (2009) Graphical and numerical evaluation of continuous glucose sensing time lag. *Diabetes Technol Ther* **11**: 139–43

DIABETES TECHNOLOGY & THERAPEUTICS

Hypoglycaemia detected more often using CGM

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓✓

1 The objective of this study was to compare the detection of hypoglycaemic episodes (defined as a blood glucose level of <70 mg/dL (<3.9 mmol/L), and a duration >15 minutes) using the FreeStyle Navigator continuous glucose monitoring (CGM) system's alarms with detection with an average of eight finger-stick blood glucose tests per day.

2 A total of 58 people with type 1 diabetes used CGM in a clinic setting for a 5-day period to assess the performance of the hypoglycaemia alarm function.

3 CGM measurements were compared with reference YSI measurements taken every 15 minutes.

4 Fingerstick glucose testing was evaluated in 91 people with type 1 diabetes in the home setting. They used the built-in glucose meter in the CGM system for a 20-day period.

5 When the alarm was activated, the reference YSI measurements confirmed that blood glucose levels were ≤85 mg/dL (≤4.7 mmol/L) 77.2% of the time.

6 The average frequency of finger-stick tests in the home setting was 7.9 tests. In those using only the finger-stick blood glucose testing to detect hypoglycaemia, a blood glucose level ≤85 mg/dL (≤4.7 mmol/L) was verified within 30 minutes at a rate of 27.5%.

7 Hypoglycaemia detected by CGM was not verified by fingerstick testing very often, even with a high frequency of fingerstick tests.

McGarraugh G, Bergenstal R (2009) Detection of hypoglycemia with continuous interstitial and traditional blood glucose monitoring using the FreeStyle Navigator continuous glucose monitoring system. *Diabetes Technol Ther* **11**: 145–50

PEDIATRIC DIABETES

Use of CGM declines over time

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓

1 This 13-week pilot study of the FreeStyle Navigator continuous glucose monitoring (CGM) system examined the feasibility of daily use in 24 children using insulin pumps and 21 using multiple daily injection (MDI) therapy with insulin glargine.

2 Participants in the insulin pump group initially used CGM slightly more than the MDI group, but use declined at a similar rate in both groups by weeks 22–26.

3 High satisfaction with the CGM system in the first weeks was associated with extended use. Decreasing use over time highlights the need for improved technologies and strategies to improve long-term use.

Diabetes Research in Children Network (DirecNet) Study Group (2009) Prolonged use of continuous glucose monitors in children with type 1 diabetes on continuous subcutaneous insulin infusion or intensive multiple-daily injection therapy. *Pediatr Diabetes* **10**: 91–6

DIABETES TECHNOLOGY & THERAPEUTICS

Automatic insulin suspension in youth

Readability	✓✓✓✓
Applicability to practice	✓✓✓
WOW! factor	✓✓✓✓✓

1 The first step towards a closed-loop artificial pancreas may be to automatically suspend insulin delivery when the integrated sensor detects that glucose levels have fallen. This system was reviewed in 17 adolescents with type 1 diabetes, using the proportional-integrative-derivative (PID) algorithm, and efficacy and safety was assessed.

2 In 8 of the 17 participants, and 34 hours of closed-loop automated insulin delivery, 18 pump suspensions ≥60 minutes occurred.

3 Sensor glucose levels fell from 159±42 mg/dL to the lowest value of 72±13 mg/dL. Plasma glucose levels fell from 168±51 mg/dL to 72±16 mg/dL. Only four of the 18 events recorded values <60 mg/dL.

5 Using the PID algorithm, automatic insulin suspension may be an effective way of preventing hypoglycaemia in young people.

Cengiz E, Swan K, Tamborlane W et al (2009) Is an automatic pump suspension feature safe for children with type 1 diabetes? An exploratory analysis with a closed-loop system. *Diabetes Technol Ther* **11**: 207–10

DIABETES TECHNOLOGY & THERAPEUTICS

CGM is acceptable in non-insulin-using adults with T2D

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓

1 Continuous glucose monitoring (CGM) was used to provide data to inform behavioural intervention techniques in sedentary non-insulin-using adults with type 2 diabetes. The authors aimed to assess the feasibility and acceptability of CGM as well as dietary and exercise teaching events.

2 A total of 27 adults used CGM for 72 hours. Data were collected by entering information (meals, exercise) into the monitor.

3 CGM graphs showed 141 dietary and 71 exercise teaching events; 82% of participants maintained a paper record of all events, and 52% reported difficulty in remembering to enter events into the monitor. Despite discomfort at the sensor site, most participants were willing to use CGM again.

4 The authors concluded that overall, CGM was acceptable and feasible, and that problems may be ameliorated by improved technology.

Allen N, Fain J, Braun B, Chipkin S (2009) Continuous glucose monitoring in non-insulin-using individuals with type 2 diabetes: acceptability, feasibility, and teaching opportunities. *Diabetes Technol Ther* **11**: 151–8

"Hypoglycaemia detected by continuous glucose monitoring was not verified by fingerstick testing very often, even with a high frequency of fingerstick tests."