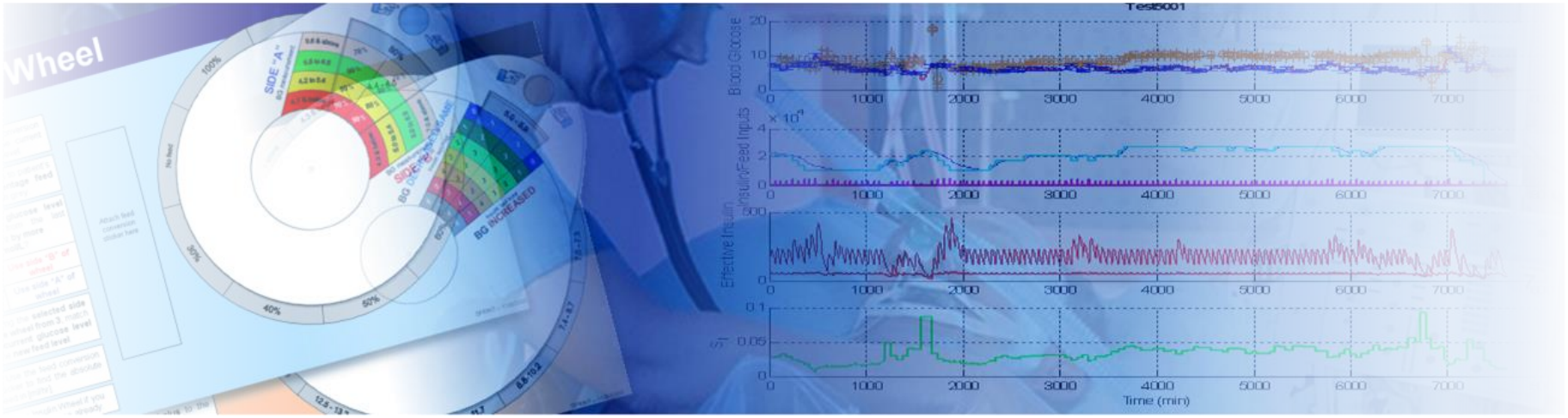
A pilot study of continuous glucose monitoring in critically ill patients:

Do they perform well enough for use in glycaemic control?



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A well known story in the ICU

- Hyperglycaemia (High Blood Sugar) is prevalent in critical care & increases mortality
  - Impaired insulin production + Increased insulin resistance = High Blood Glucose (BG)
  - Average BG values **> 10mmol/L** are not uncommon

- Tight Glycaemic Control (TGC) → better outcomes:
  - Reduced mortality ~17-43% (6.1-7.75 mmol/L) [van den Berghe, Krinsley, Chase]
  - Organ failure rate and severity reduced [Chase]
  - Savings of $1500-3000 per patient treated [van den Berghe, Krinsley]

- However, there is a catch...
  - Several studies report increased risk of hypoglycaemia
  - Optimal control requires high measurement frequency (1-2 hourly or better)
  - Most TGC studies measure blood glucose1-4 hourly, more frequently only if BG is low
  - Frequent measurement (even 1-2 hourly) uncommon due to the **clinical effort** [e.g. MacKenzie]

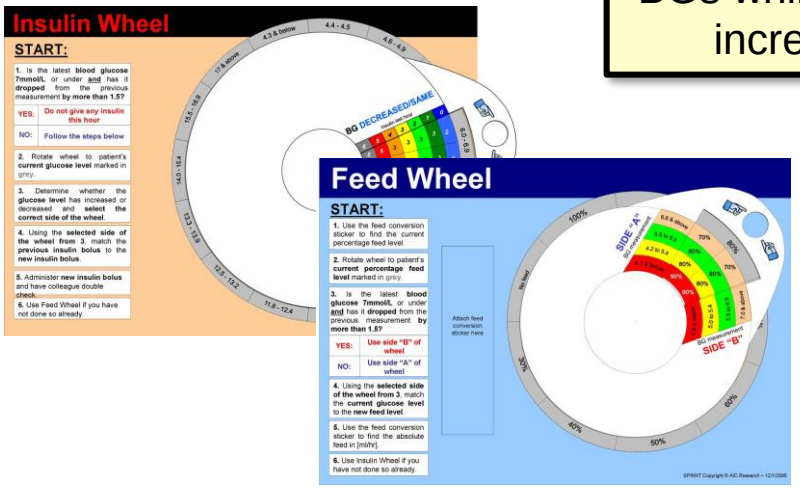
The result is extremely variable control with longer measurement intervals

TGC in Christchurch ICU

SPRINT

In August 2005, we introduced the paper based SPRINT tight glycaemic control protocol

- SPRINT achieved 86% of BG measurements within a 4.4-8.0 mmol/L band
- Mortality was reduced by up to 35%
- Reduced hypoglycaemia vs conventional
- The protocol required on average16 BG measurements per day



STAR

Over the following years, SPRINT evolved into the computer based STAR protocol (now used in ICU)

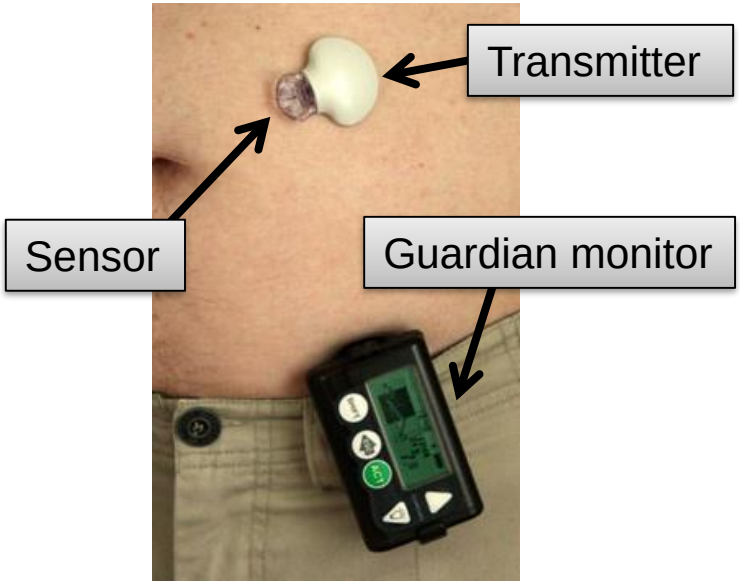
- STAR has achieved 89% of BG measurements within a 4.4-8.0 mmol/L band to date (~25 patients)
- The main advantage is the reduced hypoglycaemia from 2.9% to 0.9% (%BG < 4.0) and an expected 50% further reduction in severe hypoglycemia
- BG was measured 12 times per day on average

We would like to reduce BGs while maintaining or increasing safety

CGM devices used in this study

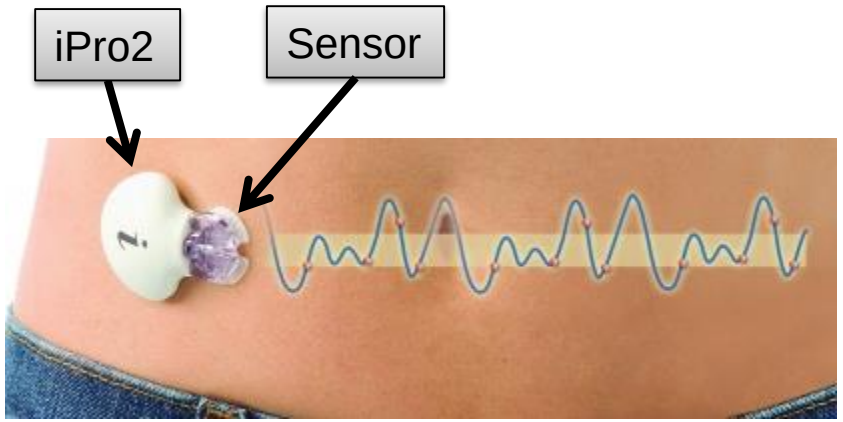
Two different CGM devices are tested in this study

Medtronic Guardian Real-Time CGM



- Uses the latest Enlite glucose sensor
- Displays real-time glucose value
- Manually enter calibration BG measurements 2-4 times daily

Medtronic iPro2 CGM



- Uses the latest Enlite glucose sensor
- Stores sensor glucose internally
- Calibration BG measurements must be recorded at least every 8 hours

*Figures sourced from Google for explanatory purposes only

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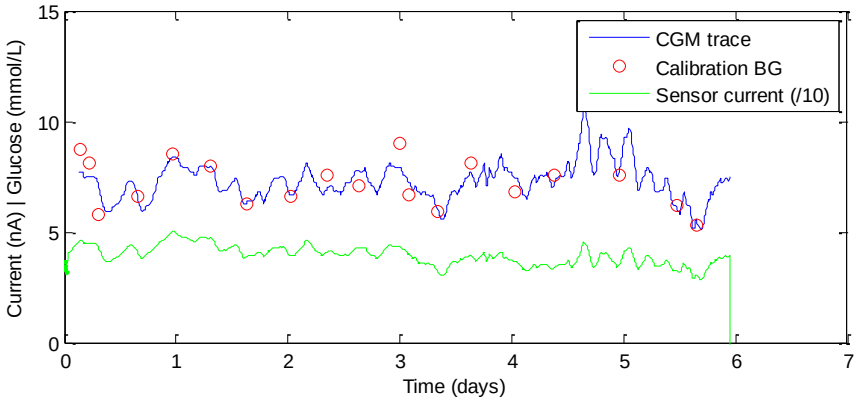
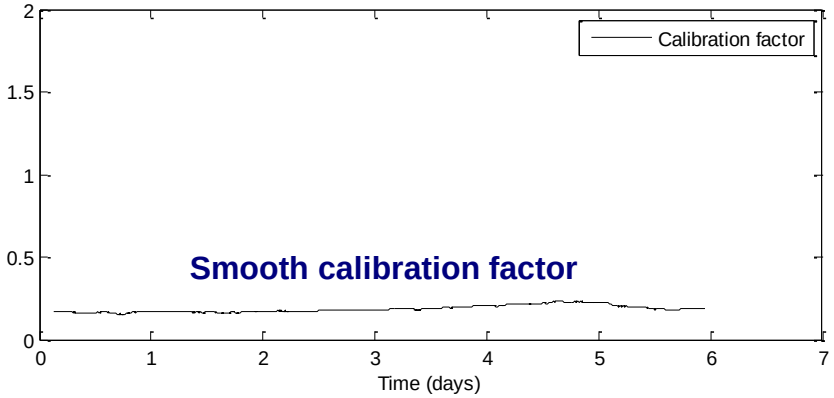
Calibration algorithms

Retrospective Calibration

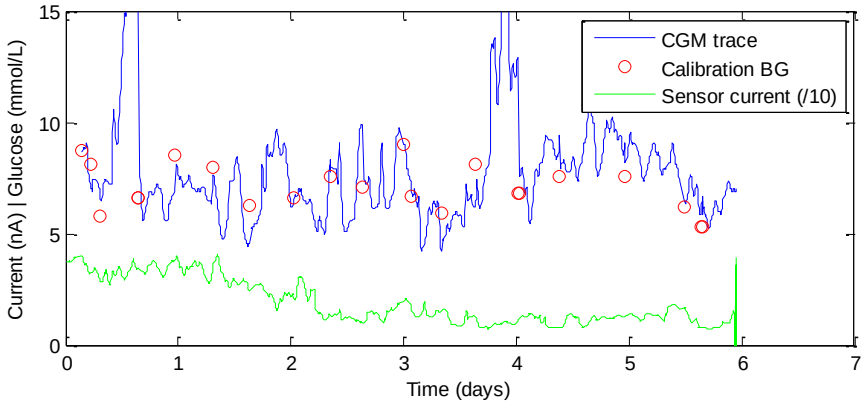
Calibration occurs after monitoring has finished. The algorithm can use all data to produce a CGM trace from the sensor current and BGs

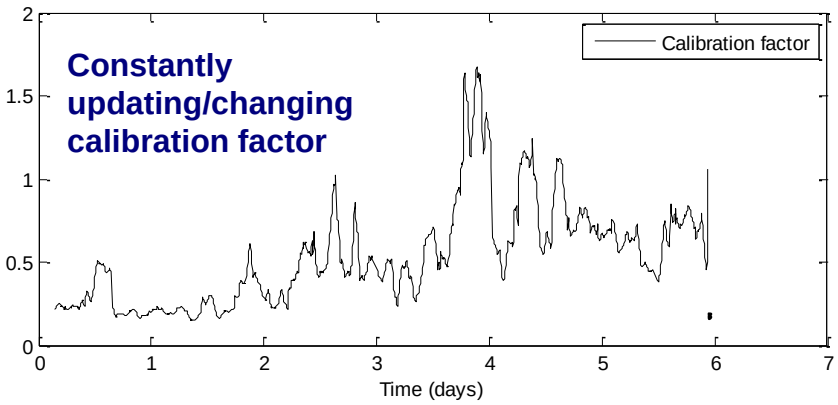




Real-time Calibration

Only data that has already been recorded can be used for calibration, so the calibration factor constantly updates and projects forward





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Pilot Clinical Trial

Aim: Assess inter-site variability, inter-device/calibration variability and overall reliability of CGM

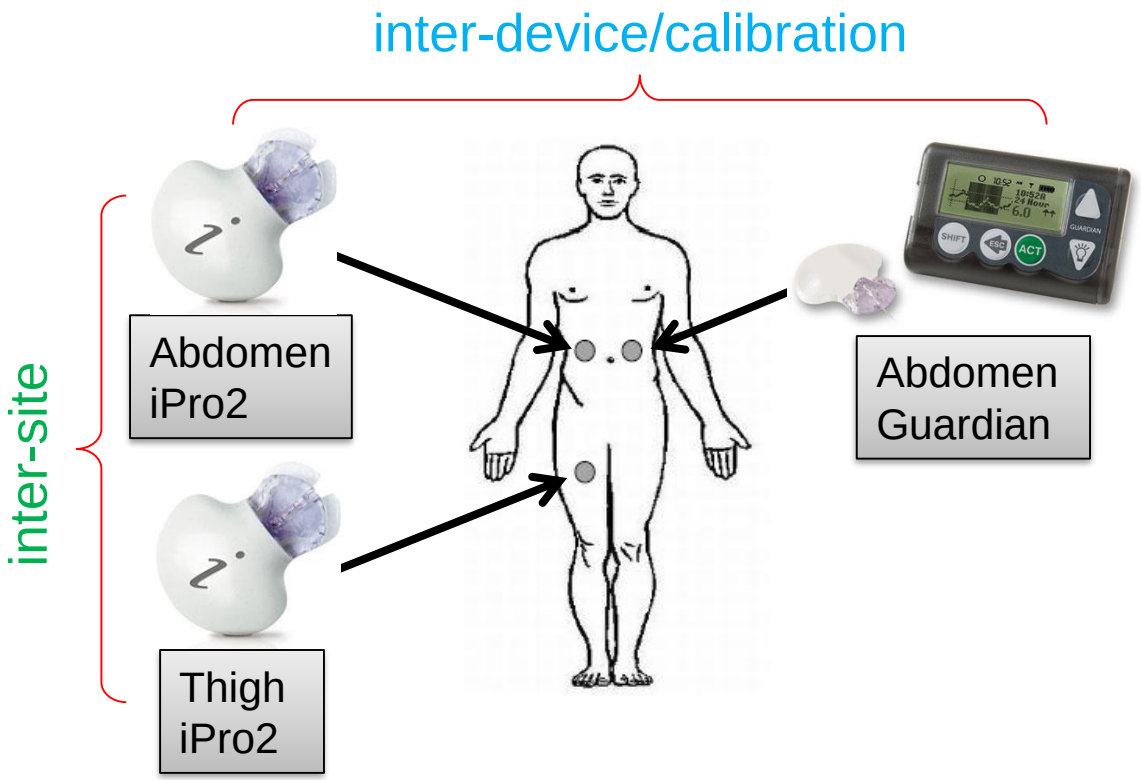
Devices: Medtronic Guardian real-time and Medtronic iPro2 – both using Medtronic Enlite sensors

Duration: Up to 6 days of CGM monitoring, while on the STAR glycaemic control protocol

Cohort

Patients	10
Age (years)	51 [39 - 64]
Sex (M/F)	5/5
APACHE II	24 [17 - 27]
APACHE III	85 [52 - 99]
SAPS II	52 [30 - 59]
LOS (days)	20 [10 - 33]
Outcome (L/D)	6/4
Diabetes (None/T1/T2)	10/0/0

Device locations



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Overall Results

BG results			
Number of patients	10		
BG interval (hours)	1.5 [0.9 - 2.3]		
Blood glucose (mmol/L)	6.9 [6.2 - 7.6]		
CGM results	*Guardian - Ab.*	*iPro2 - Ab.*	*iPro2 - Th.*
Number SG Data sets	10	10	10
Duration of CGM (days)	4.8 [3.0 - 6.0]	4.8 [2.8 - 6.0]	5.3 [3.0 - 6.0]
Cal BG interval (hours)	7.5 [5.1 - 8.2]	7.5 [3.6 - 9.0]	6.3 [3.0 - 8.1]
Ref BG interval (hours)	1.8 [1.0 - 2.8]	1.7 [1.0 - 2.7]	1.8 [1.0 - 2.8]
Sensor glucose (mmol/L)	6.9 [5.9 - 8.1]	6.7 [6 - 7.4]	6.7 [6.1 - 7.3]
MARD (%)	24.0	11.8	12.4

Typically > 3 days monitoring per patient

Frequent reference BG measurements for assessing CGM performance

Guardian vs. iPro2 difference in performance 24% vs. 11.8%

Abdomen vs. Thigh difference in performance 11.8% vs. 12.4%

Accuracy at different BG levels

Abdomen Guardian Bland Altman plot shows that error is dependent on glucose level.

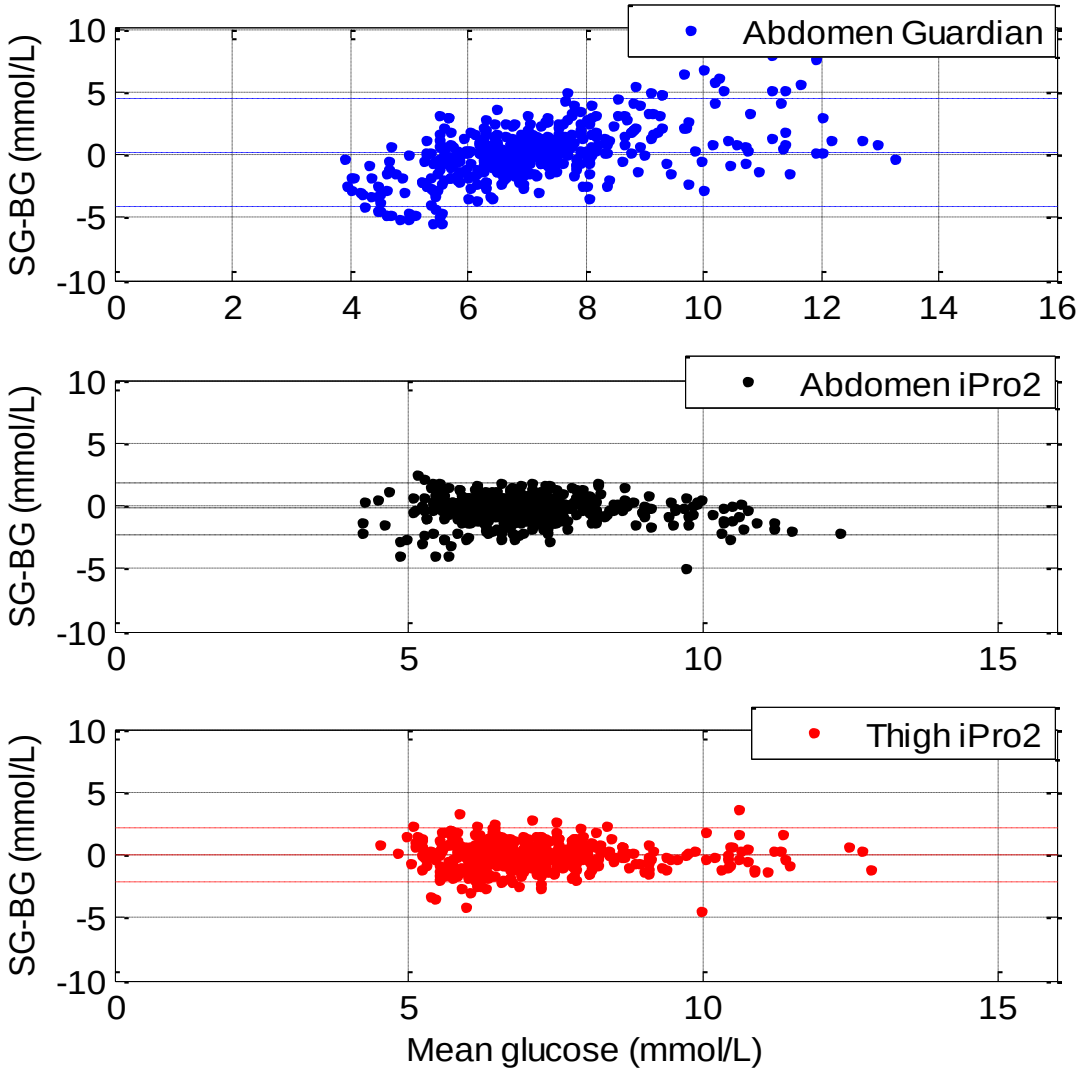
CGM tends to read below BG at low glucose and above BG at high glucose

Abdomen iPro2 Bland Altman plot shows that error is not dependent on glucose level.

Lower error compared to the Guardian CGM

Thigh iPro2 Bland Altman plot shows that error is also not dependent on glucose level.

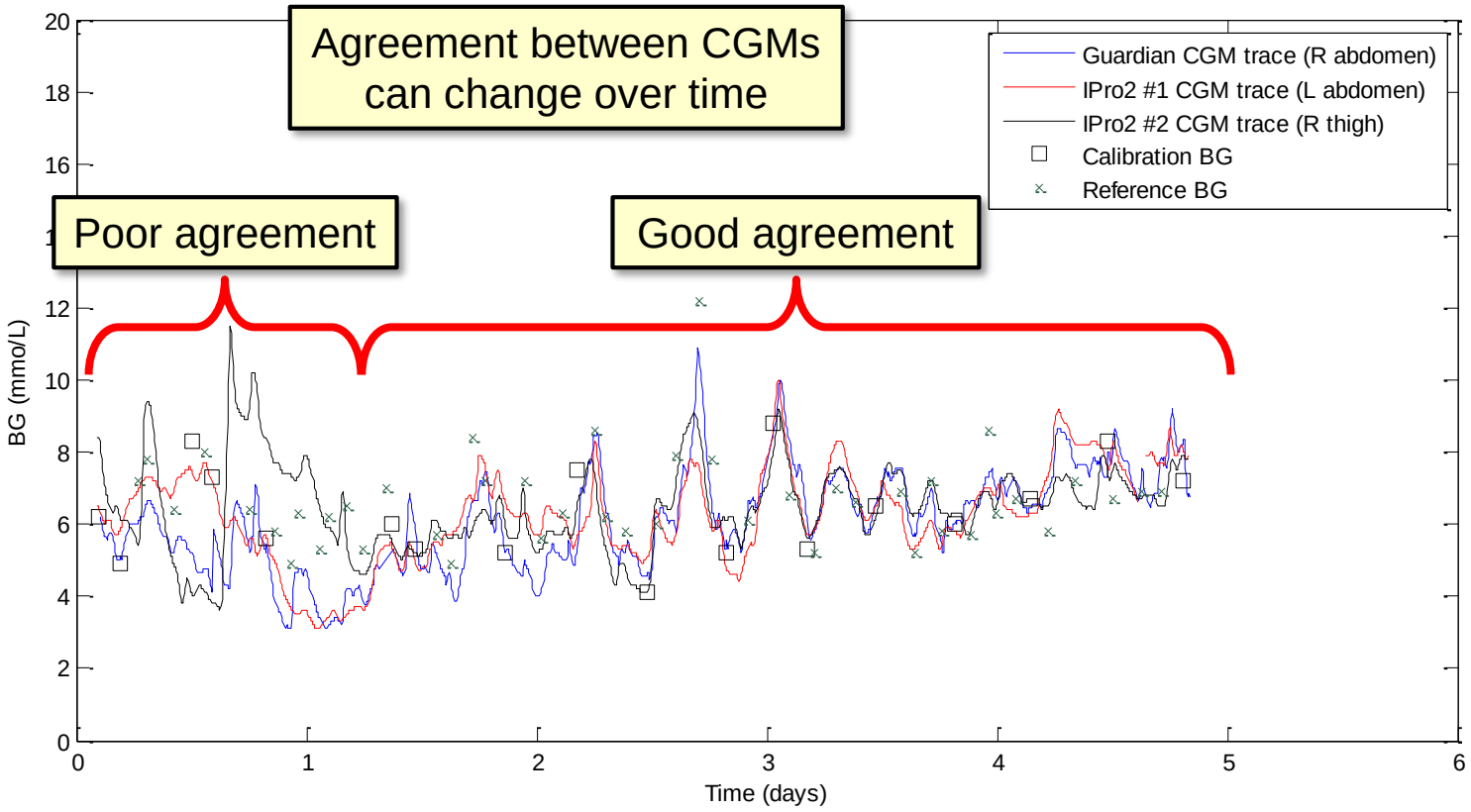
Similar error profile to Abdomen iPro2



Case Study – No oedema

Patient had very little (if any) extra fluid on board

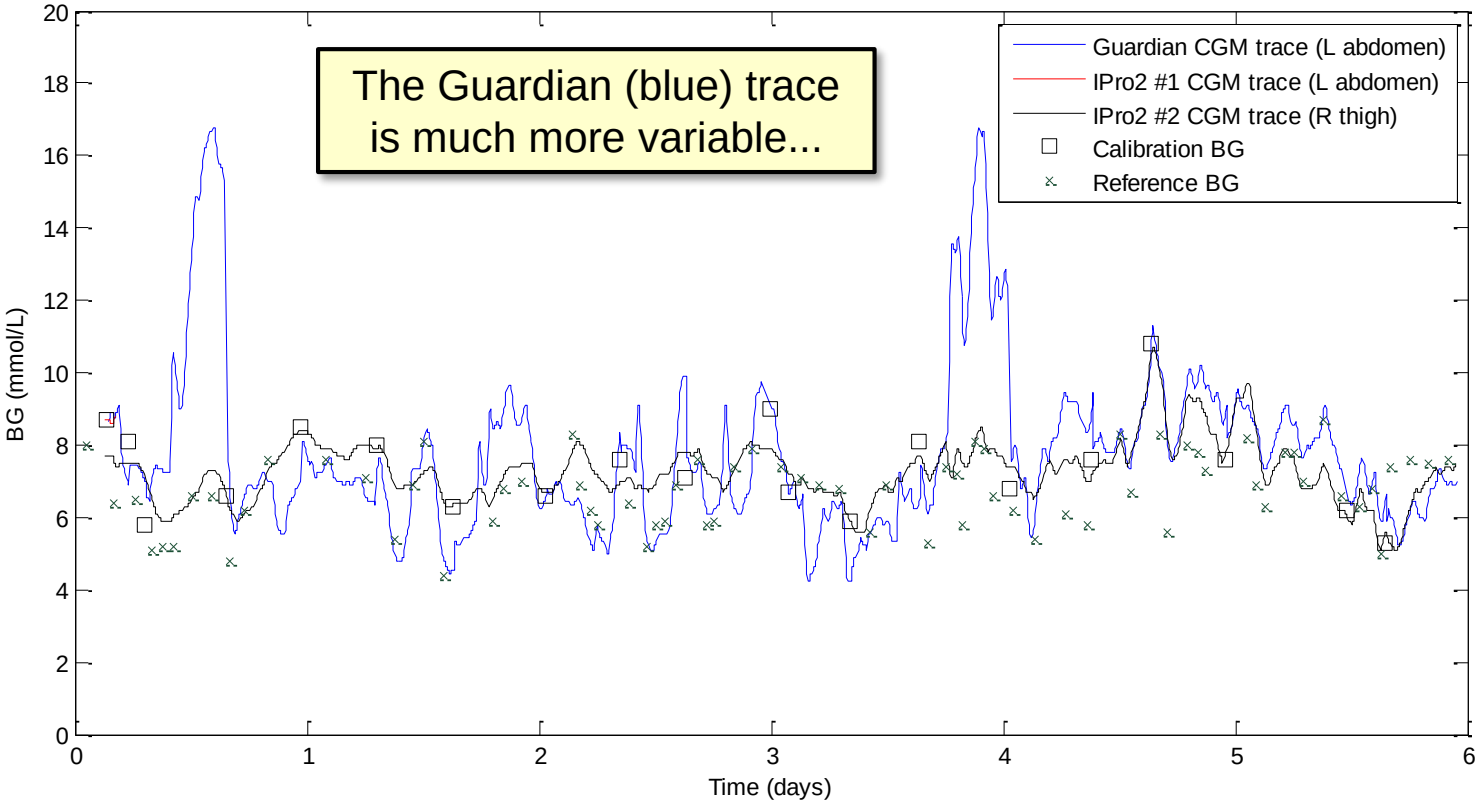
- The three sensors were very easy to insert and stayed in place for the duration of the study
- We obtained three full CGM traces
- Day 1 differences may be due to sensor initial calibration or wetting issues, or ??? The thigh iPro2 sensor is the one different. Abdomen is consistent. Could also be motion?



Case Study – Severe oedema

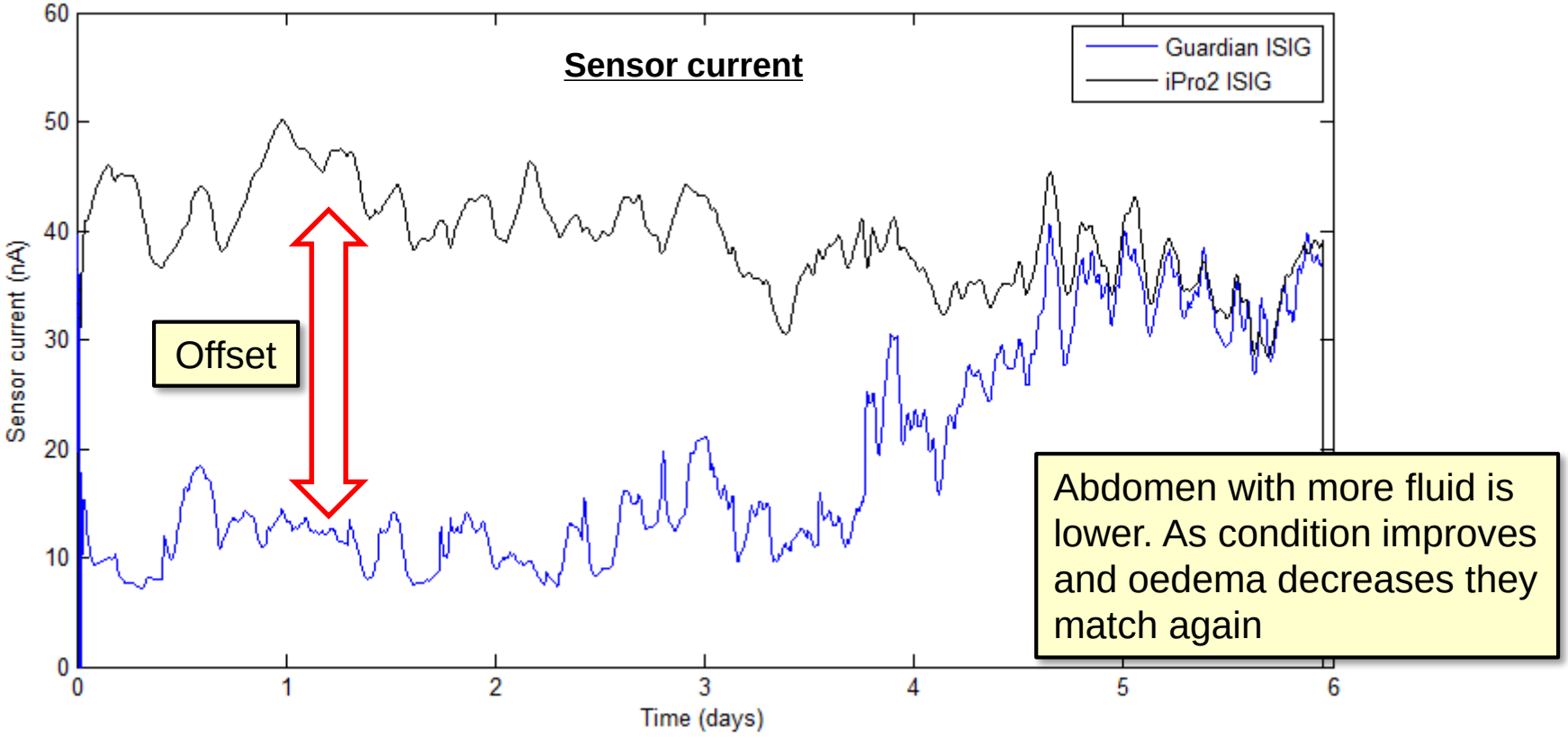
Patient was ~55kg's, but had ~18 Litres of (estimated) extra fluid on board

- Clinical challenge → trying to keep the sensor base attached skin
- The leaking fluid was so bad, we lost one out of the three sensors immediately after insertion (cannot re-insert), and after replacing, we lost a second sensor in a matter of hours
- Blue trace (Guardian) → abdomen, black trace (iPro2) → thigh



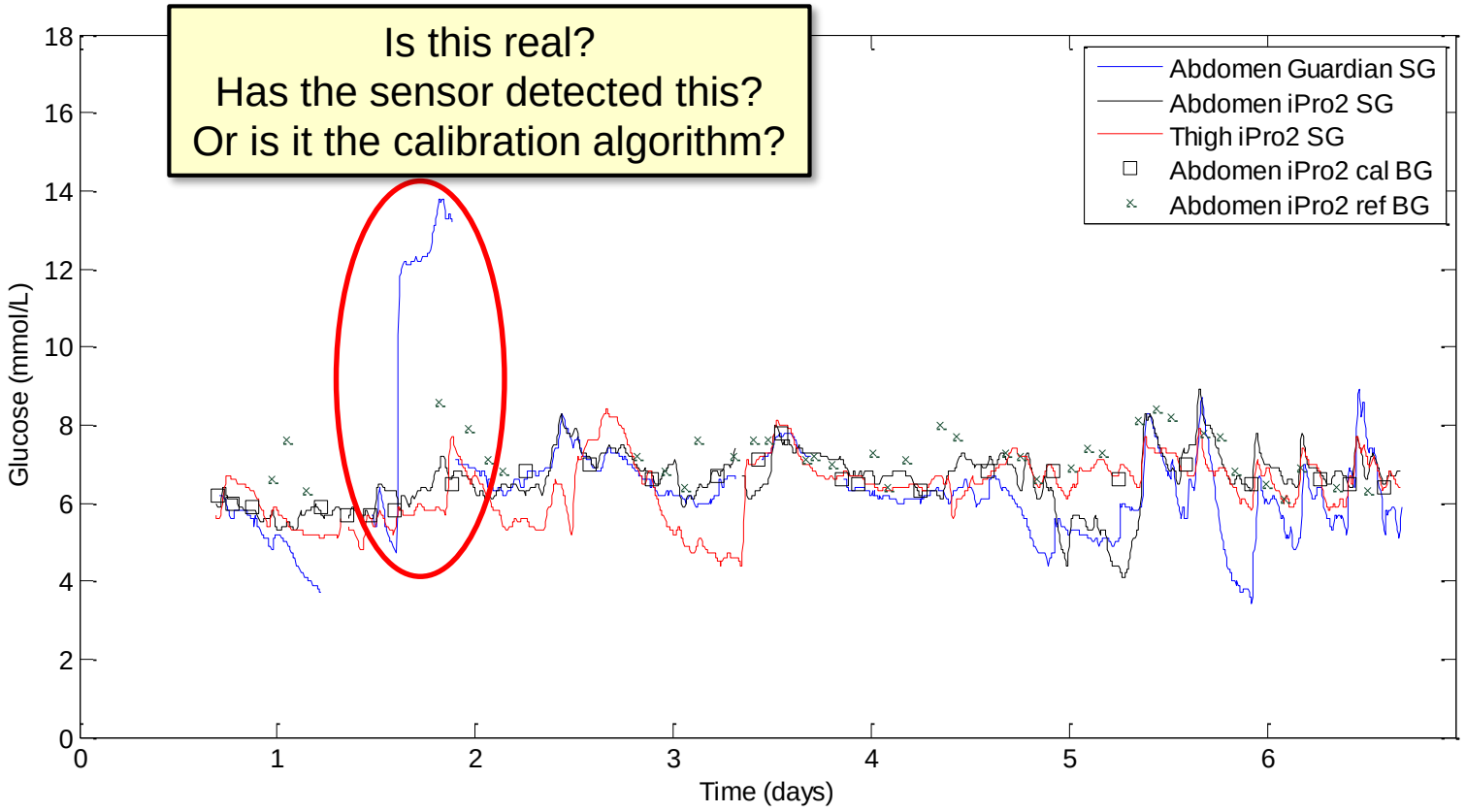
Case Study – Severe oedema

- If we look at the raw sensor output (electrical current) we get a ‘fair’ comparison with the calibration removed (the sensor hardware is the same)
- Several day offset could be due to low sensitivity or oedema ‘diluting’ glucose concentration
- As patient condition improves, blue sensor signal increases (day 3 onward)



Sensor/Calibration artefacts

- If CGMs are also to be used with a TGC protocol, the algorithm should be aware of anomalies in the trace → we don't want to dose insulin off incorrect measurements
- Other studies have previously reported **false CGM hypoglycaemic events due to pressure** being applied to the sensor



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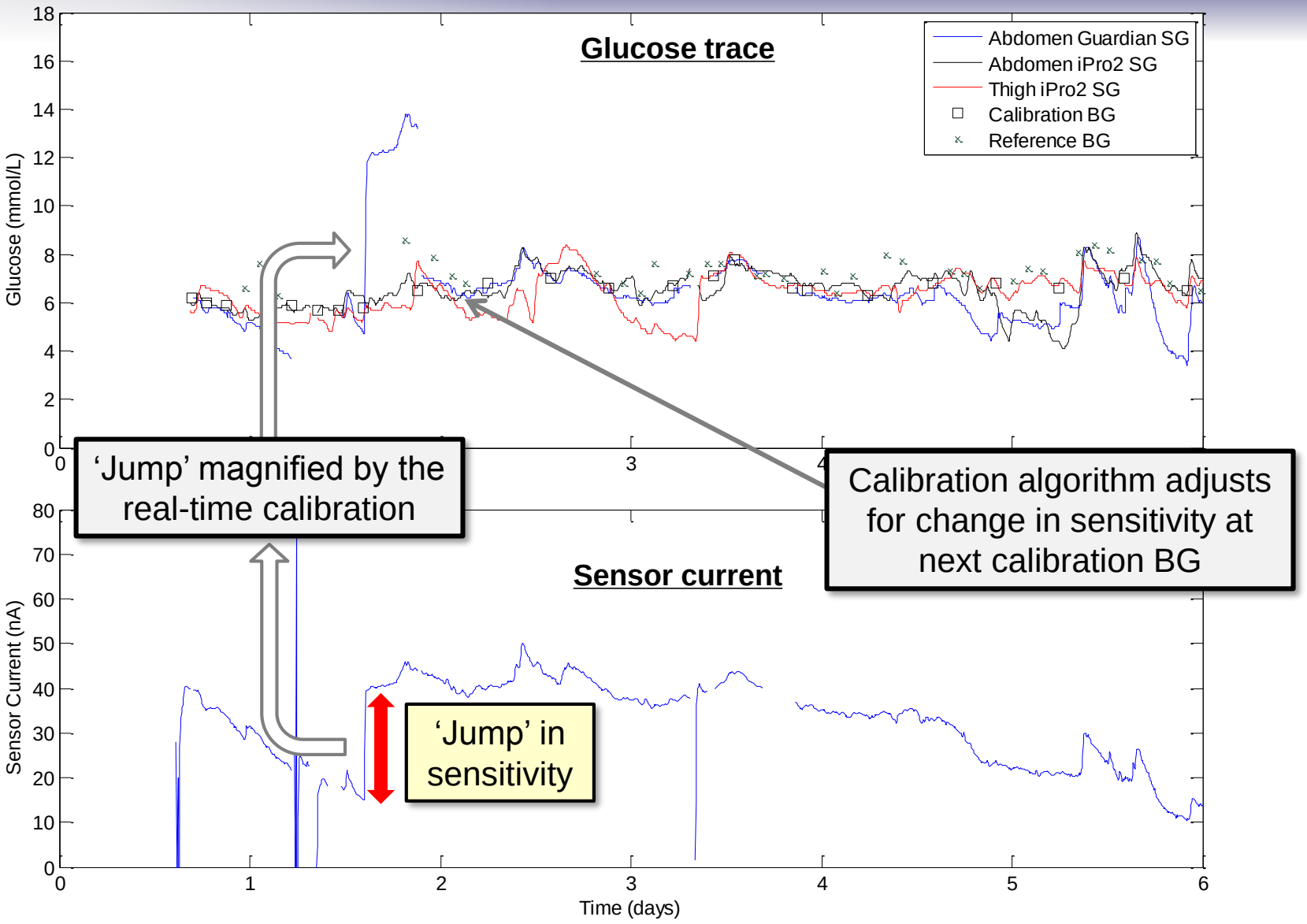
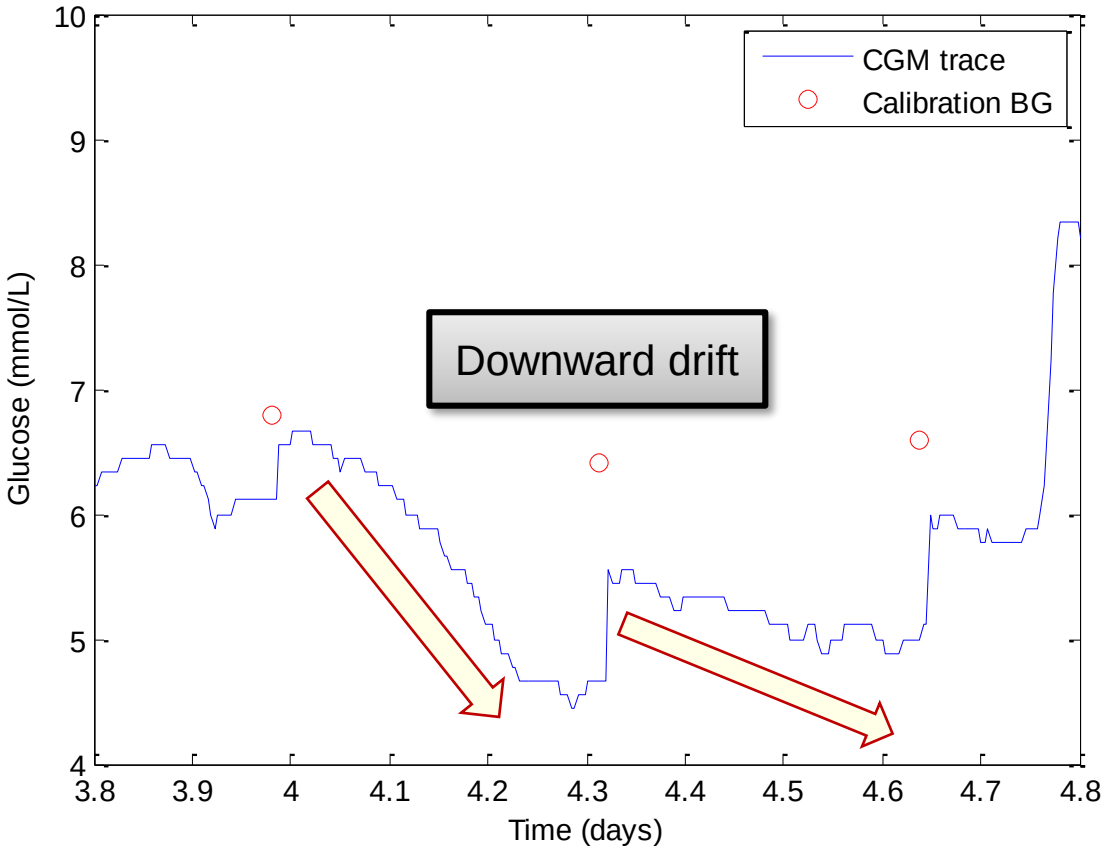
Sensor/Calibration artefacts



Drift in real-time calibration



Sensor and/or calibration drift is a phenomenon that can occur when using a real-time calibration algorithm

When the next calibration measurement is entered into the device, it ‘jumps’ to correct some of the drift.

Drift could result in severe mistreatment if not managed properly when using CGM to dose insulin

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Summary

This pilot study investigated the reliability of two CGM devices in the Christchurch ICU

Key things we have learnt:

- First and most importantly, CGMs can perform very well in some critically ill patients
- Device calibration can have a significant affect on CGM accuracy (retro better than RT)
- Sensor location has negligible affect on CGM output in those patients without oedema
- Oedema can make monitoring difficult for both the clinical staff and the device
- Sensor artefacts or changes in sensitivity do occur and there could be many causes
- Drift can occur when using a real-time device and needs to be properly managed if CGMs are used for TGC or to dose insulin

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Ongoing work

In light of these findings, we are now conducting a follow on clinical trial of CGM devices.

The current trial will enrol 60 patients and is using the latest CGM technology, designed specifically for hospital use.

The trial has three phases, designed to answer:

1) What effect does oedema and/or sepsis have on CGM performance?
2) Are alarms useful when monitoring critically ill patients?
3) Can CGM be used successfully as the ‘sensor’ for the STAR TGC protocol?

To date we have enrolled 30 patients and we are planning to reach 60 by the end of 2014

For those interested, results will be published in the not so distant future…

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Acknowledgement

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Thank you for listening
Any questions?