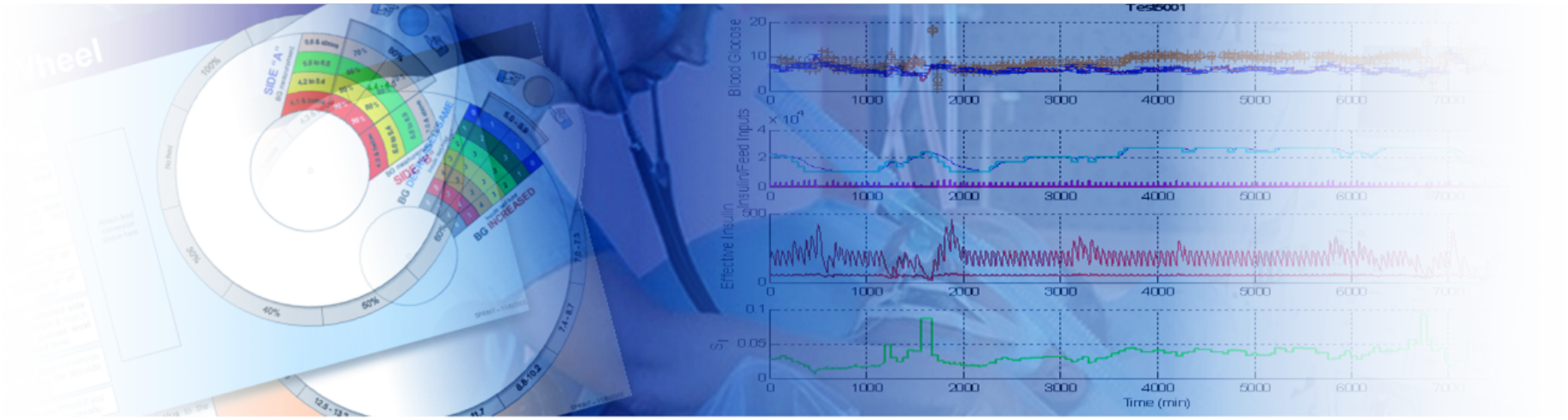
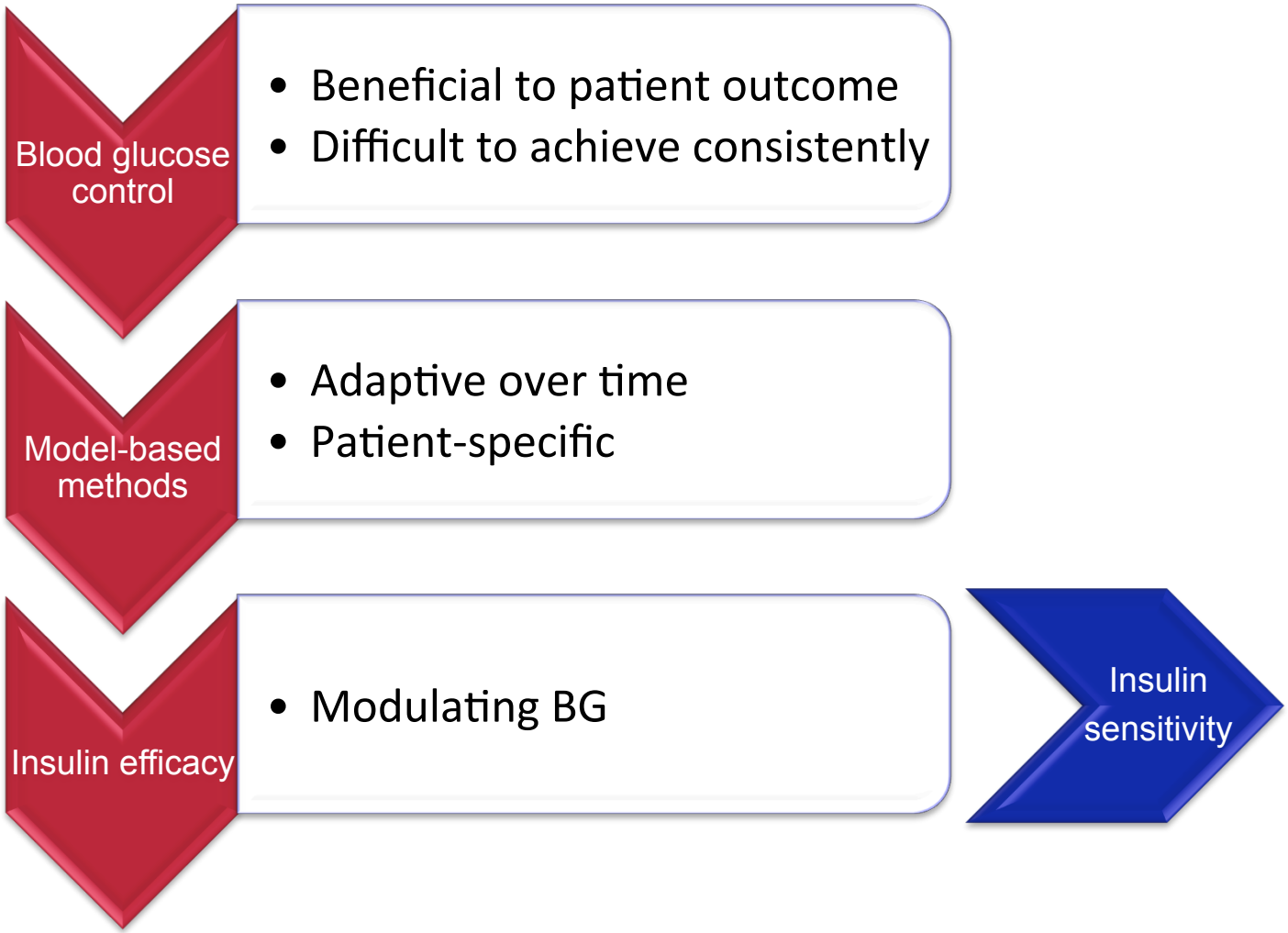
Impact of sensor and measurement-timing errors on model-based insulin sensitivity



Christopher Pretty
Cardiovascular Research Centre
University of Liège
Belgium

Preliminaries

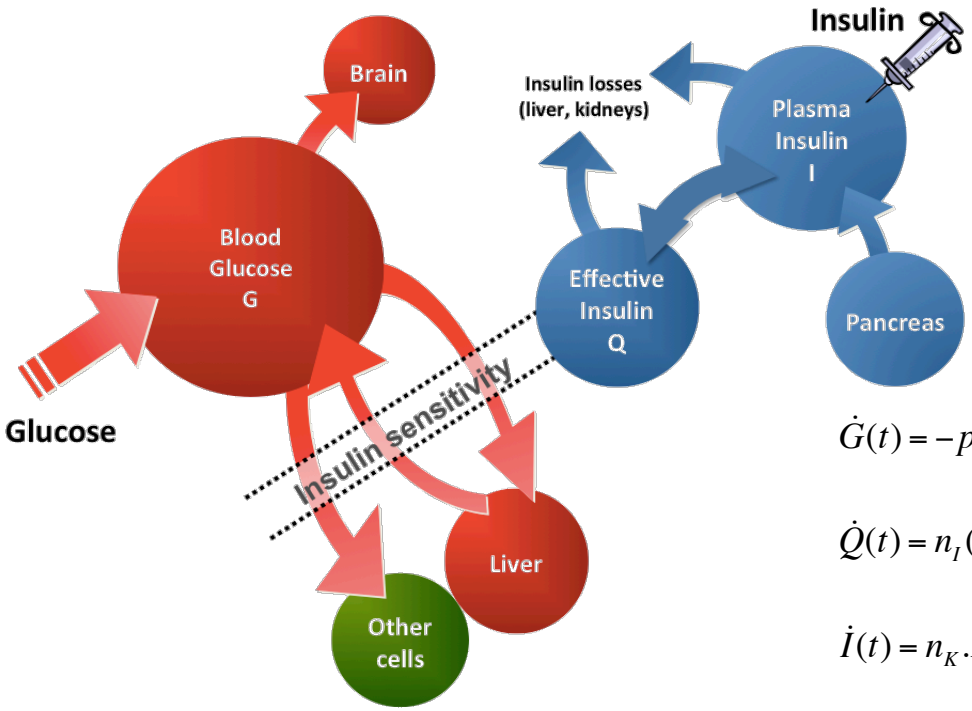
- Intensive care unit:



How is such a crucial parameter affected by measurement errors??

Glucose-Insulin model

- There are many different variations on the glucose-insulin system model.
  - All are (as far as I am aware) compartment models.
  - Given the similarity of most of these models, the results presented may generalise to a degree.



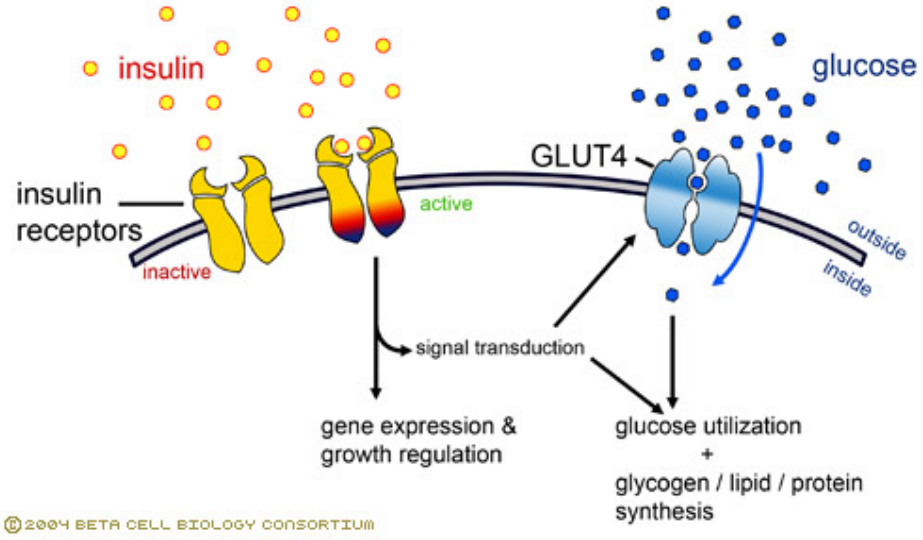
$$\dot{G}(t) = -p_G.G(t) - SI(t).G(t)\frac{Q(t)}{1+\alpha_G Q(t)} + \frac{P(t)+EGP-CNS}{V_G}$$

$$\dot{Q}(t) = n_I(I(t)-Q(t)) - n_C\frac{Q(t)}{1+\alpha_G Q(t)}$$

$$\dot{I}(t) = n_K.I(t) - n_L\frac{I(t)}{1+\alpha_I I(t)} - n_I(I(t)-Q(t)) + \frac{u_{ex}(t)}{V_I} + (1-x_L)\frac{u_{en}(I)}{V_I}$$

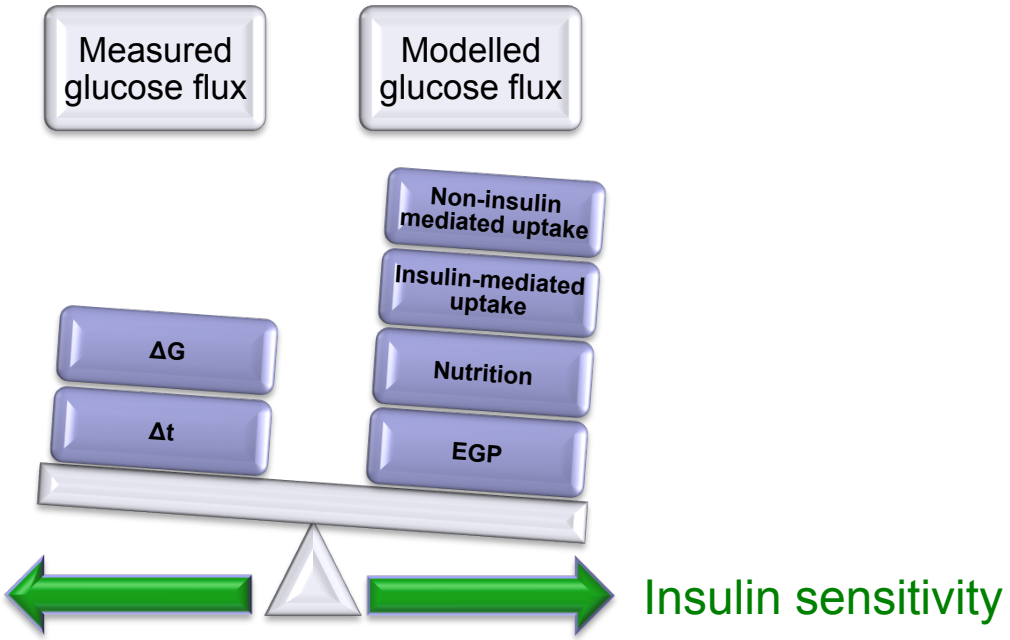
Relevance

- Insulin sensitivity
  - The insulin sensitivity parameter (SI) describes/captures the patient-specific glycaemic response to insulin.
  - The specific form of parameter is model-dependent.
  - Identification methods vary, but rely heavily on blood glucose (BG) measurements.
  - Thus BG measurement error and timing impact insulin sensitivity and consequently, the quality of glycaemic control.



Insulin sensitivity

- Identification
  - The insulin sensitivity parameter (SI) is identified by balancing the measured glucose flux through the G compartment.



  - Thus, errors in specifying the time points, *t*, or the measured concentrations, *G*, directly impact SI – But by how much??

Method of investigation

- Monte Carlo analysis
  - Using clinical data from 270 SPRINT patients.
  - Adding simulated errors to the BG measurements and timing intervals.
  - Re-fitting the insulin sensitivity parameter with these errors.
  - Quantifying the results

N	270
Age (years)	65 [49-73]
Gender (M/F)	165/105
Operative/Non-Operative	104/166
Hospital mortality (%)	27%
APACHE II score	19 [16-25]
APACHE II ROD (%)	30 [17-53]
Diabetic status (T1DM/T2DM)	10/34
ICU length of stay (hrs)	160 [77-346]

Timing error

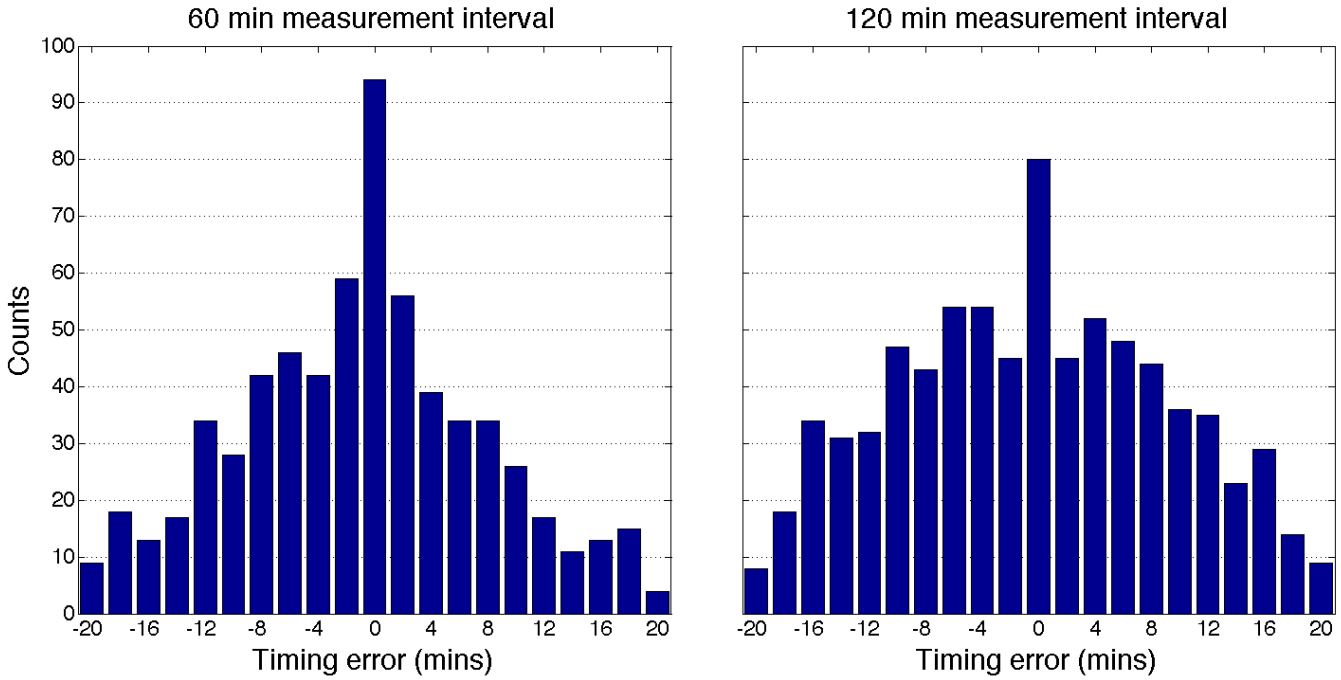
- More of an issue for non-computerised protocols
  - Such as SPRINT.
  - Glycaemic data recorded by hand and assigned to hourly time points.

ICP										
CPP										
Serum K+										
Blood Glucose			19.7	18.4		13.7	14.4	4.7	11.1	8.8
Fluid between hours of 6–	07	08	09	10	11	12	13	14	15	16
actrapid 50/50 500ml					5	0	5	5	5	0
D5W (1/L KCl 20)				40		40	40	40	40	40
DASIGN &										
domperidone										

- Can still have an impact through the stochastic models used in STAR
  - Stochastic models derived from SPRINT data are used to characterise the dynamic behavior of SI.

Timing error

- Error model
  - Clinical data from the STAR protocol trials was recorded both on paper, as usual and by the computerised controller.
  - Together, these data provide information about BG timing errors.



BG sensor errors

- Glucometer errors are relatively large

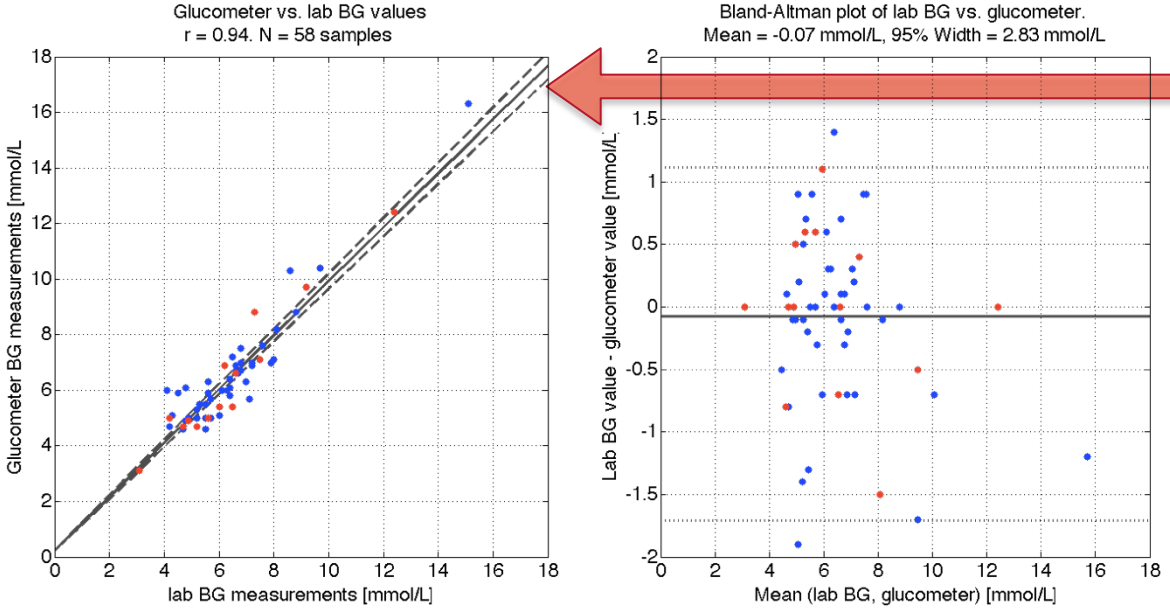
- Thought to be worse in critically ill patients
  - Haematocrit
  - Interfering substances
  - PaO_2
- Published error data from Manufacturers is obtained under optimum conditions.
- From 17 Patients on the SPRINT protocol, we have laboratory BG measurements – indicative results only.

BG sensor errors

- Manufacturers published uncertainty (Arkray Inc.)

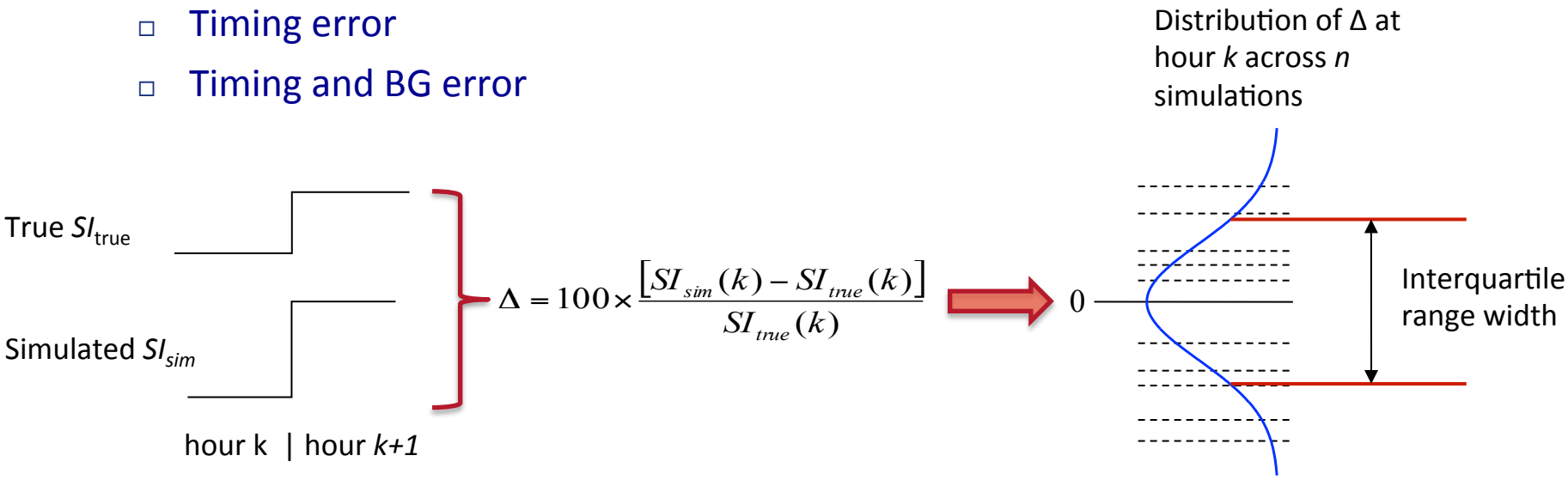
Blood glucose (mmol/L)	4.3	6.9	21.0
Bias (%)	+2.1	+0.2	-2.0
Precision, CV (%)	3.5	2.8	2.7

- Christchurch ICU paired measurements



Quantifying effects on SI

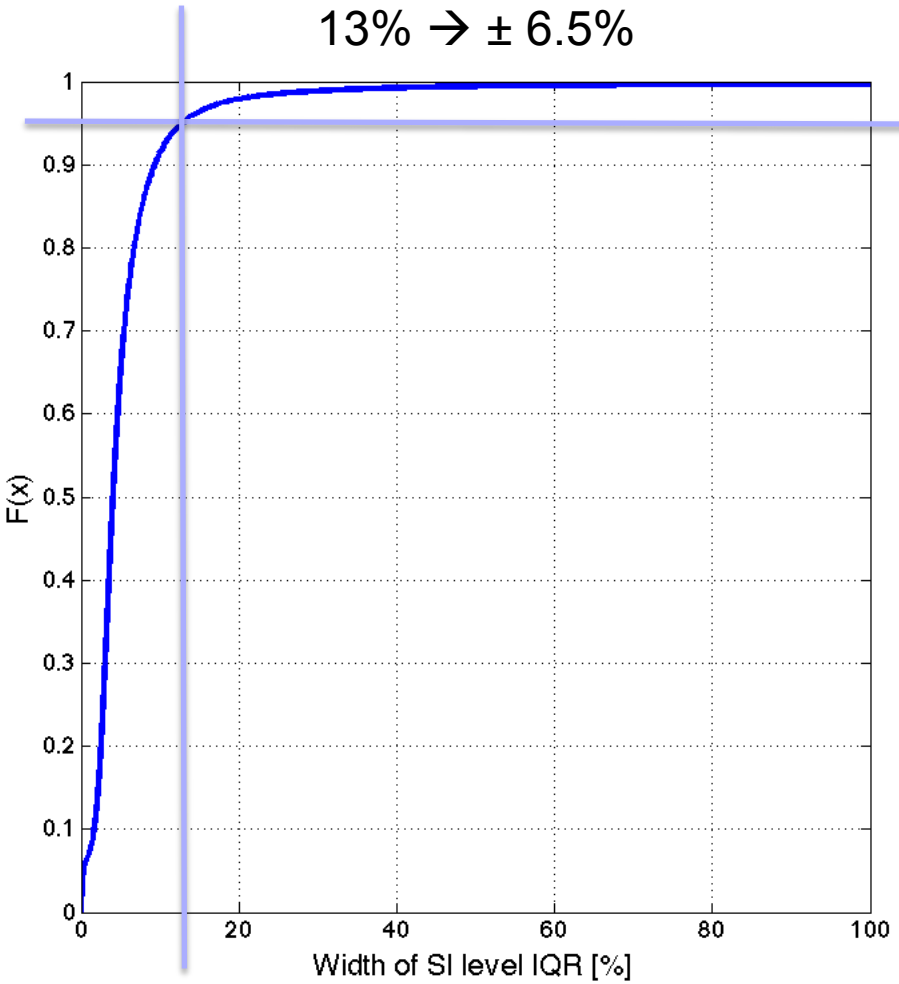
- Compare 'actual' SI to 'noisey' SI using Monte Carlo simulations
  - BG error
  - Timing error
  - Timing and BG error

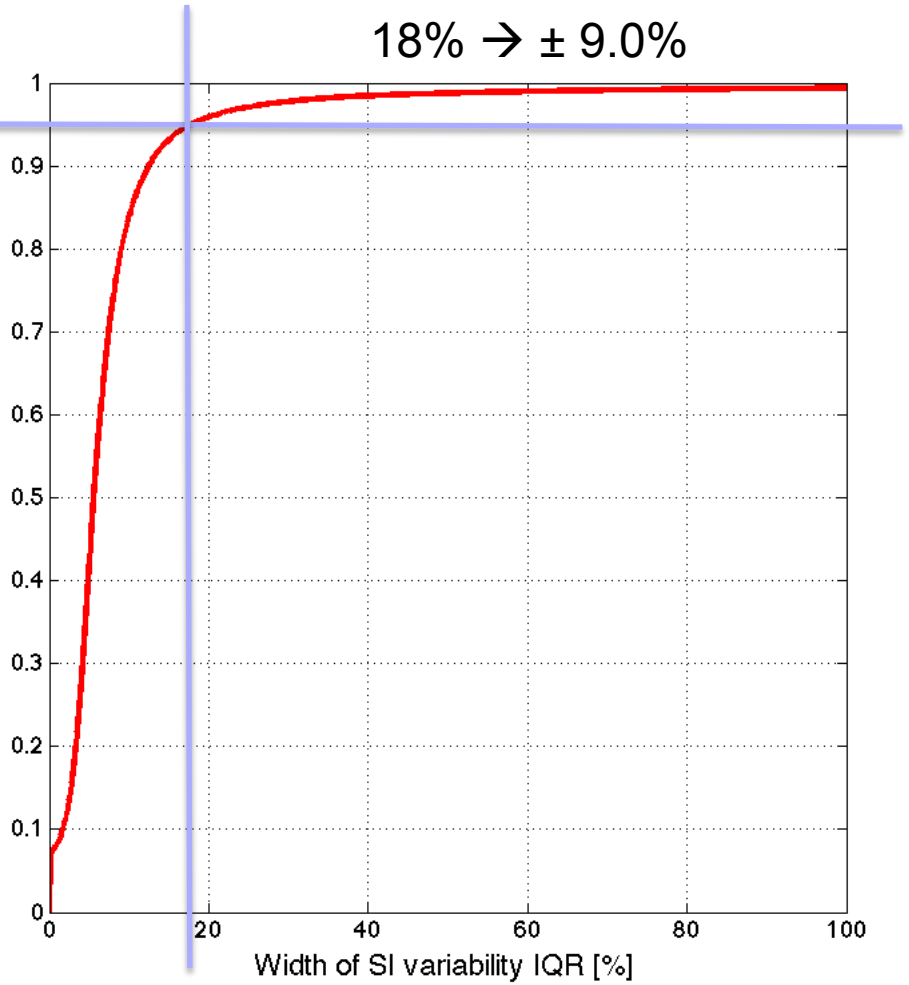


- Compare hour-to-hour changes in SI similarly

Results

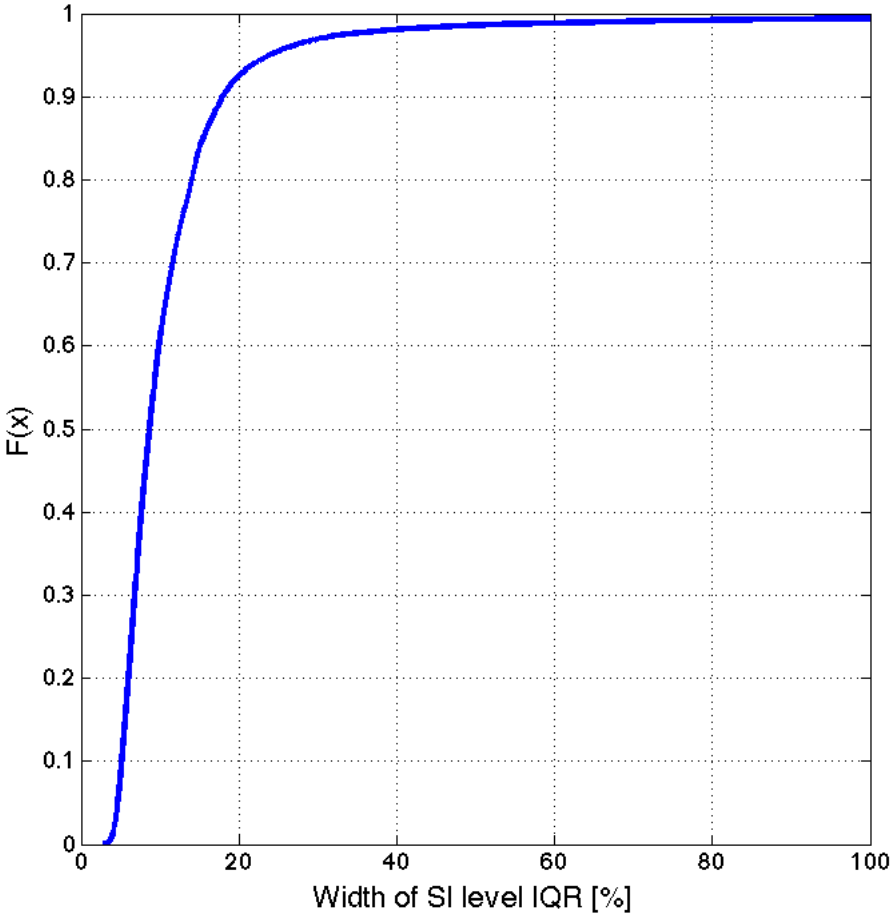
- Timing error only
  - Very limited impact

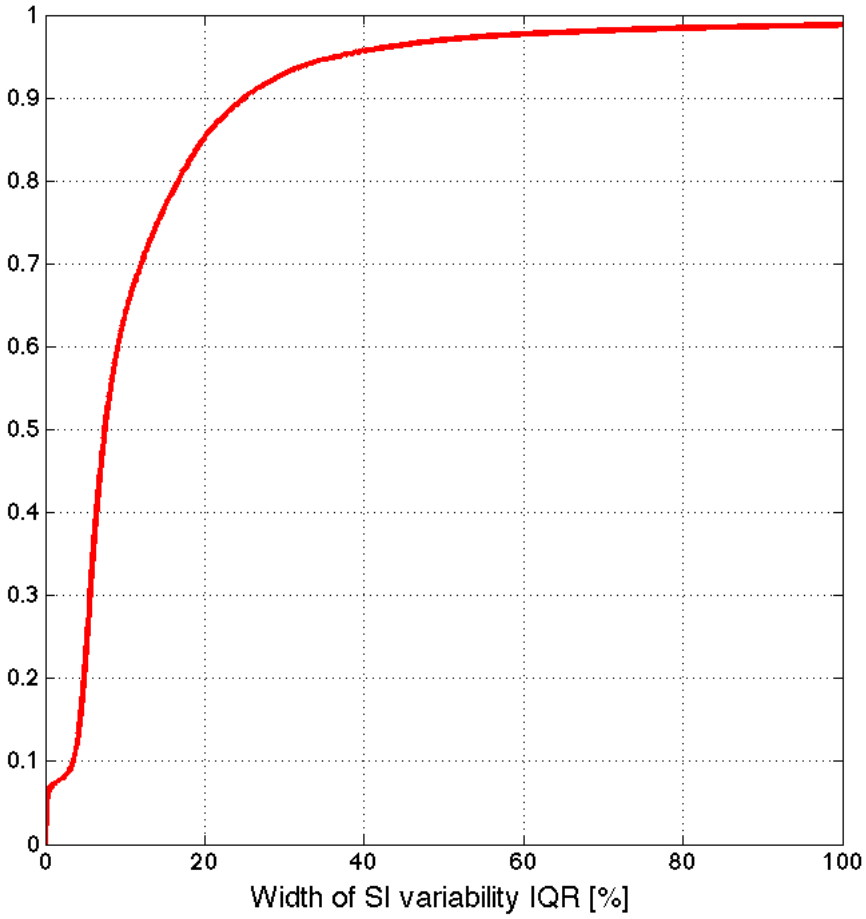




Results

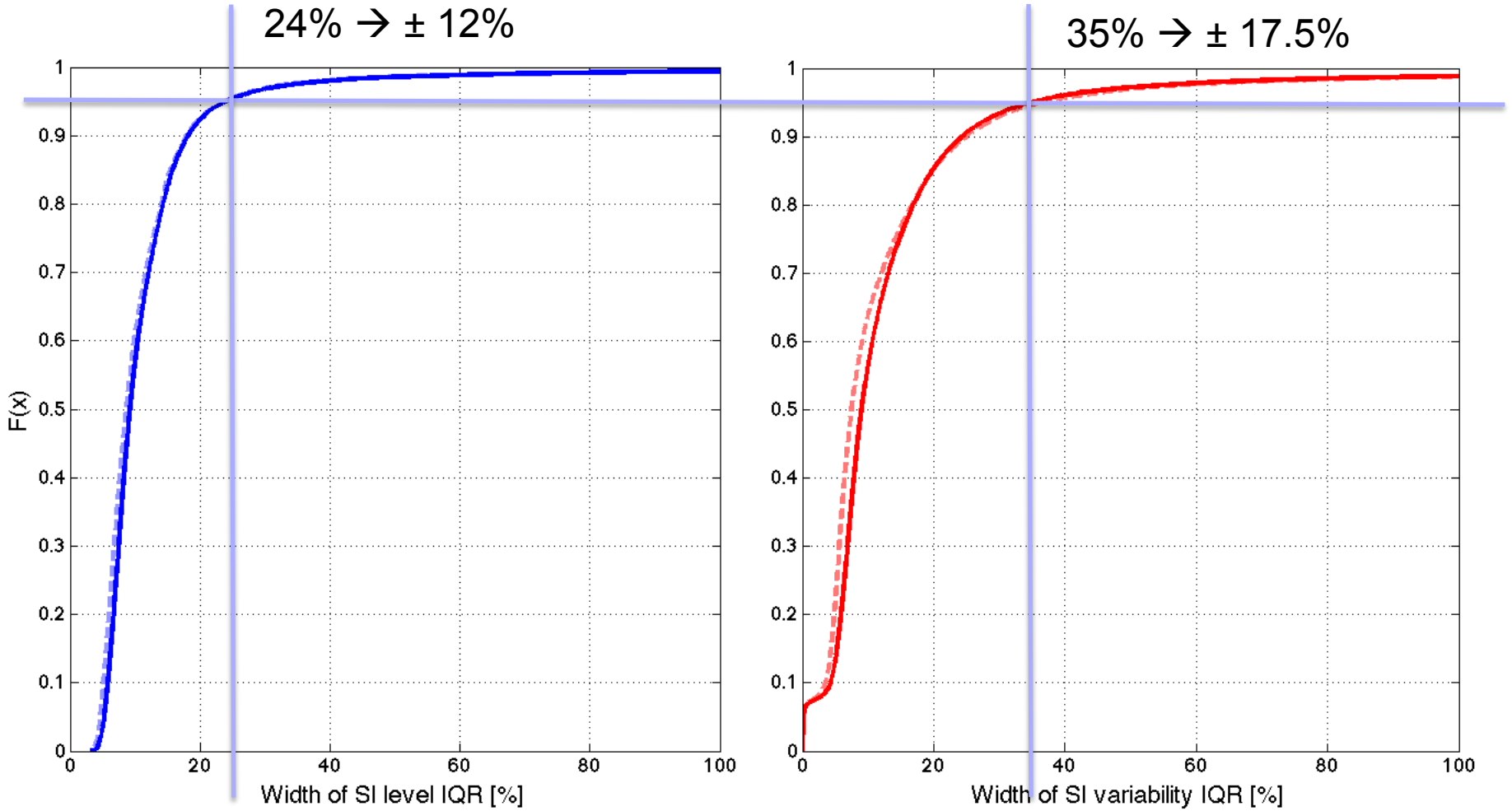
- Manufacturers BG error only





Results

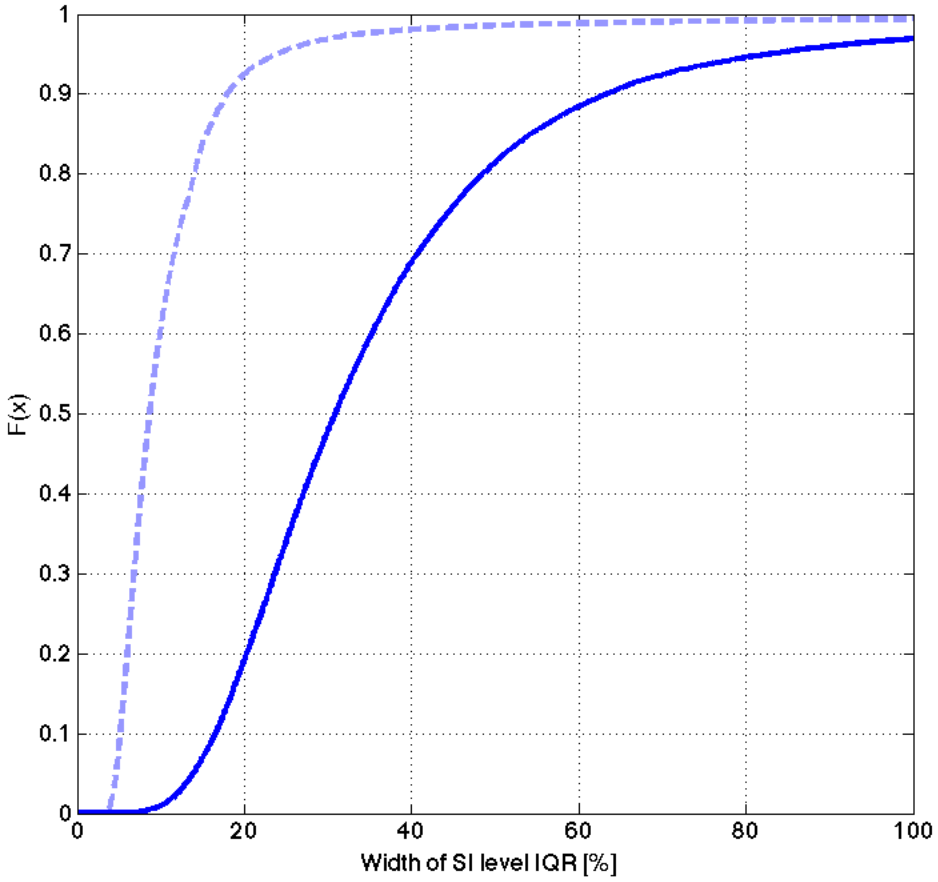
- Manufacturers BG error and timing error combined

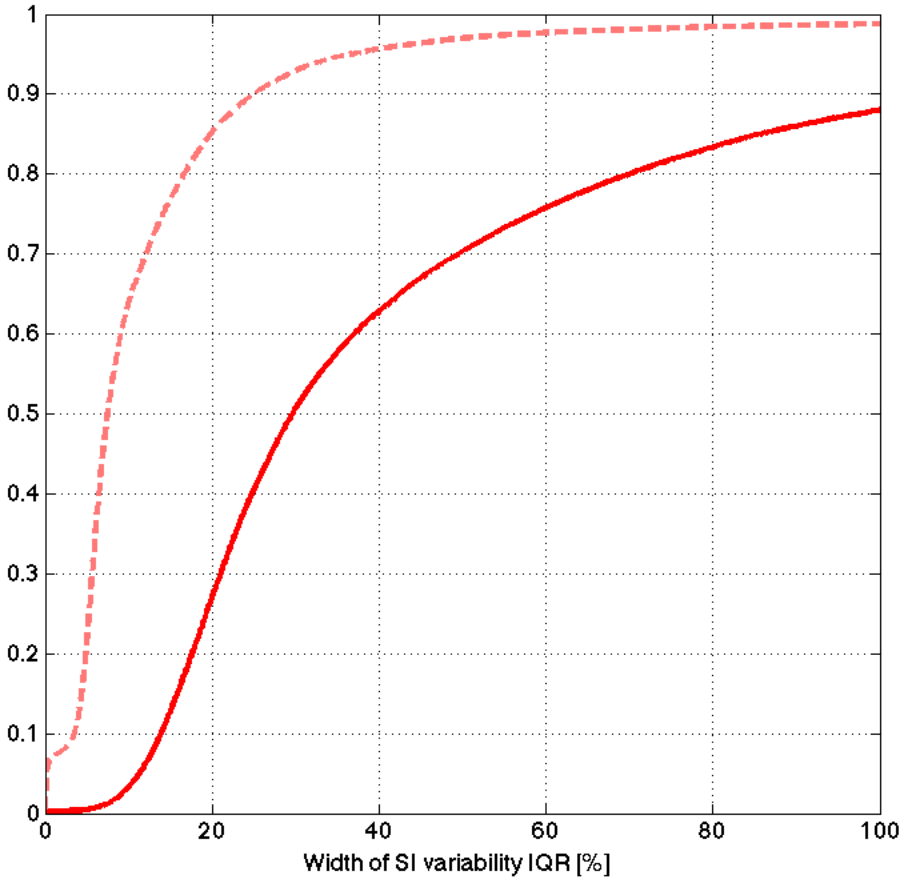


Results

- ICU BG error model

Blood glucose (mmol/L)	4.3	6.9	21.0
Bias (%)	+1.0	+1.2	+1.4
Precision, CV (%)	16	10	3





Implications

- Manufacturers glucometer error model
  - Variability in SI level is not too bad
  - Variability in hour-to-hour changes may be problematic
    - 63% of all 'true' hour-to-hour changes were within ±17.5%
  - Will necessitate caution in using SI as a diagnostic marker
    - Time averaging may help
  - Overall, errors of this nature are unlikely to have a significant clinical impact during glycaemic control

- ICU BG error model
  - Indicative only!!! → too few reliable data points at this stage
  - However, if this error model is realistic, there is a significant room for improvement in glycaemic control by using better sensors.

Conclusions

- Measurement timing errors
  - Have a relatviely small effect on identified insulin sensitivity.
  - Not clinically significant.

- BG measurement errors
  - Assuming the uncertainty reported by the manufacturer, the impact on SI level is probably not clinically significant in terms of glycaemic control.
  - But, the impact on the hour-to-hour changes in SI may be significant.

    → Implications for use of SI as a diagnostics marker

  - If the uncertainty hinted at by the paired measurments from the Christchurch ICU is realistic, the impact on SI is large.

    → Improvements in glycaemic control by using better sensors

- Questions?