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

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Intensive care unit:

- Blood glucose control:
  - Beneficial to patient outcome
  - Difficult to achieve consistently

- Model-based methods:
  - Adaptive over time
  - Patient-specific

- Insulin efficacy:
  - Modulating BG

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

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

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

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

<table>
<thead>
<tr>
<th>N</th>
<th>270</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>65  [49-73]</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>165/105</td>
</tr>
<tr>
<td>Operative/Non-Operative</td>
<td>104/166</td>
</tr>
<tr>
<td>Hospital mortality (%)</td>
<td>27%</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>19 [16-25]</td>
</tr>
<tr>
<td>APACHE II ROD (%)</td>
<td>30 [17-53]</td>
</tr>
<tr>
<td>Diabetic status (T1DM/T2DM)</td>
<td>10/34</td>
</tr>
<tr>
<td>ICU length of stay (hrs)</td>
<td>160 [77-346]</td>
</tr>
</tbody>
</table>
• More of an issue for non-computerised protocols
  - Such as SPRINT.
  - Glycaemic data recorded by hand and assigned to hourly time points.

• 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.
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.
- Glucometer errors are relatively large

- Thought to be worse in critically ill patients
  - Haematocrit
  - Interfering substances
  - PaO₂

- 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.
- Manufacturers published uncertainty (Arkay Inc.)

<table>
<thead>
<tr>
<th>Blood glucose (mmol/L)</th>
<th>4.3</th>
<th>6.9</th>
<th>21.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bias (%)</td>
<td>+2.1</td>
<td>+0.2</td>
<td>-2.0</td>
</tr>
<tr>
<td>Precision, CV (%)</td>
<td>3.5</td>
<td>2.8</td>
<td>2.7</td>
</tr>
</tbody>
</table>

- 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

\[ \Delta = 100 \times \left( \frac{SI_{sim}(k) - SI_{true}(k)}{SI_{true}(k)} \right) \]

- Compare hour-to-hour changes in SI similarly
Results

- Timing error only
  - Very limited impact
    - 13% $\rightarrow \pm 6.5\%$
  - $18\% \rightarrow \pm 9.0\%$
Results

- Manufacturers BG error only
Manufacturers BG error and timing error combined

24% \( \rightarrow \pm 12\% \)

35% \( \rightarrow \pm 17.5\% \)
ICU BG error model

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</thead>
<tbody>
<tr>
<td>Bias (%)</td>
<td>+1.0</td>
<td>+1.2</td>
<td>+1.4</td>
</tr>
<tr>
<td>Precision, CV (%)</td>
<td>16</td>
<td>10</td>
<td>3</td>
</tr>
</tbody>
</table>

![Graphs showing the relationship between width of SI level IQR and function f(\%)](image)

![Graph showing the relationship between width of SI variability IQR and function f(\%)](image)
**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 relatively 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 measurements from the Christchurch ICU is realistic, the impact on SI is large.
    - Improvements in glycaemic control by using better sensors
Questions?