Model-based Insulin Sensitivity and Pharmacodynamic (PD) Surfaces

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Background and Aims

The main methods for determining insulin sensitivity with high resolution are either clinical (hyperinsulinemic eu- or hyper-glycemic clamp) or model-based (e.g. FSIWGGT). Typically, the model-based methods use some form of the Minimal Model (MM), which has been shown to underestimate insulin sensitivity in some cases.

This research presents a method of analysing a model's PD surface to determine:
- If its fundamental dynamics capture clinical behaviours
- What, if any, dynamics are missing from a model
- What, if any, dynamics are not necessary

There is currently no fixed method for doing such an analysis and most models are validated on the ability to fit time trajectories of patient-specific clinical data. This approach tests the ability of a model to capture data and trends (in steady state) across an entire PD surface.

Methodology

Four clinically validated models are analysed:
- Minimal Model (MM)
- Two non-linear dynamic models (ND1 and ND2)

Two sets of euglycemic and hyperglycemic clamp data are used:
- Data Set #1: Eu- and hyper- glycemic clamps are used to find a set of population parameters for each model (N=77)
- Data Set #2: Euglycemic clamp data from a lower insulin sensitivity cohort (N = 146) are used to see if the fitted models from step #1 can fit by just shifting the insulin sensitivity parameter (A model validation test)

Results and Conclusions

Performance Metrics:
- RMS Error (RMS)
- Absolute Mode of Error (AME)
- Frequency of Error Near Zero (FNZ)

Data Set #1 Results:

<table>
<thead>
<tr>
<th>Model</th>
<th>Values</th>
<th>RMS</th>
<th>FNZ (μL)</th>
<th>Scaled S&lt;sub&gt;2&lt;/sub&gt;</th>
<th>Prior S&lt;sub&gt;2&lt;/sub&gt;</th>
<th>a&lt;sub&gt;0&lt;/sub&gt;</th>
<th>a&lt;sub&gt;1&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>ND1</td>
<td>a&lt;sub&gt;0&lt;/sub&gt; = 1.47 L/mL, a&lt;sub&gt;1&lt;/sub&gt; = 0.1 L/mmol</td>
<td>0.56</td>
<td>54</td>
<td>1.2e-4</td>
<td>1.0e-4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>N2</td>
<td>a&lt;sub&gt;0&lt;/sub&gt; = 1.47 L/mL, a&lt;sub&gt;1&lt;/sub&gt; = 0.1 L/mmol</td>
<td>0.85</td>
<td>61</td>
<td>0.40</td>
<td>1.0</td>
<td>1.0e-4</td>
<td>1/6</td>
</tr>
<tr>
<td>MM</td>
<td>a&lt;sub&gt;0&lt;/sub&gt; = 0.001 L/mL, a&lt;sub&gt;1&lt;/sub&gt; = 0.001 L/mmol</td>
<td>0.95</td>
<td>61</td>
<td>0.40</td>
<td>1.0</td>
<td>1.25e-4</td>
<td>1/6</td>
</tr>
</tbody>
</table>

Data Set #2 Results: Scaling Insulin Sensitivity

- MM under predicts insulin sensitivity. MM at low insulin sensitivity provides the wrong trend result. These match reported results.
- Saturation dynamics play an important role in providing good fits across PD surface.
- Trend prediction is also reliant on the use of (at least) effective insulin saturation, which the MM does not have.
- Approach can complement typical fitting and prediction validation methods and provide information on which dynamics are necessary or sufficient in any similar model.