Interstitial insulin kinetic parameters for a 2-compartment insulin model with saturable clearance

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Glucose-Insulin system models are useful and interesting!

- Used for glycaemic control (ICU + diabetes) and diagnosis (diabetes)

The insulin sub-model is obviously a very important part

Physiologically, insulin mediates most glucose uptake from the interstitium

But... Insulin is delivered to plasma

Transport kinetics link the two
- It is common to use two insulin compartments in modelling
  - Plasma
  - Interstitium/effect compartment

- Two compartments can adequately model the behaviour of insulin seen in experiments

- Our model aims to accurately capture the actual concentration of insulin in the interstitium.
  - Rather than using an abstract ‘insulin effect compartment’ concept.
  - Permits verification by physical measurement.
Interstitial insulin kinetics impact identified insulin sensitivity (SI)

- Interstitial insulin kinetics determine how much interstitial insulin is available to mediate glucose disposal – thus, directly impacts SI.

- Previous values were taken from C-peptide kinetic data by Van Cauter et al.

- Published data from microdialysis studies offered the opportunity to directly identify the transport parameter values.

\[ n_i \] Interstitial insulin $Q(t)$ determined how much is available to mediate glucose disposal – thus, directly impacts SI.

Previous values were taken from C-peptide kinetic data by Van Cauter et al.

Published data from microdialysis studies offered the opportunity to directly identify the transport parameter values.

'Effective insulin' available for glucose disposal.
The principle of microdialysis

- Syringe pump
- Perfusate
- Dialysate – for collection and analysis
- Semi-permeable membrane
- Cell
- Interstitial fluid
- Capillary
Published studies

- 6 published microdialysis studies
- 12 datasets

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Method</th>
<th>Study Population</th>
<th>N</th>
<th>Interstitial sampling location</th>
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</thead>
<tbody>
<tr>
<td>Jansson et al. (1993)</td>
<td>Euglycaemic-hyperinsulinaemic clamp</td>
<td>Healthy non-obese</td>
<td>5</td>
<td>Abdominal subcutaneous fat</td>
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<td>Castillo et al. (1994)</td>
<td>Euglycaemic-hyperinsulinaemic clamp</td>
<td>Healthy: Body fat &lt;=12%</td>
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<td>Subcutaneous lymph vessel; lower leg</td>
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<td>Euglycaemic-hyperinsulinaemic clamp</td>
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<td>Subcutaneous lymph vessel; lower leg</td>
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<tr>
<td>Sjostrand et al. (2002)</td>
<td>Euglycaemic-hyperinsulinaemic clamp</td>
<td>Healthy lean</td>
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<td>Forearm muscle</td>
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<td>Herkner et al. (2003)</td>
<td>Oral glucose tolerance test</td>
<td>Healthy lean</td>
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<td>Mid thigh muscle</td>
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Methods

- **Identifying insulin kinetic parameters**
  - Microdialysis studies provide simultaneous plasma ($I$) and interstitial ($Q$) insulin concentrations.
  - These data combined with the model for interstitial insulin enable $n_I$ and $n_C$ to be identified by minimising errors.

\[
\dot{Q}(t) = n_I (I(t) - Q(t)) - n_C \frac{Q(t)}{1 + \alpha G Q(t)}
\]
Identifying insulin kinetic parameters

- Using measured plasma concentrations as the input

\[ Q(t) = n_I \frac{I(t)}{1 + \alpha_G Q(t)} \]
Grid search

- Minimise error over the parameters $n_I$ and $\gamma$ where:

$$\gamma = \frac{n_I}{n_I + n_C}$$

- The parameter $\gamma$ provides a more intuitive insight to the relative interstitial insulin concentration than $n_C$
  - Steady-state ratio of concentrations

Error treatment

Each study weighted equally

Per-study

Each error value weighted equally

Per-measurement
Two very different qualities of fit

Castillo et al. (1994)  
(body fat 13-21%)

Herkner et al. (2003)  
(OGTT)
Error surfaces

Each error value weighted equally

Minimum: \((n_I, \gamma) = (0.0052, 0.48)\)
Selected: \((n_I, \gamma) = (0.0060, 0.50)\)

Each study weighted equally

Minimum: \((n_I, \gamma) = (0.0066, 0.45)\)
Selected: \((n_I, \gamma) = (0.0060, 0.50)\)

Increasing error
Choice of values

\( \gamma = 0.5 \)

- \( n_I = n_C \)
- Consistent with previous value and literature

\( n_I = 0.006 \text{ min}^{-1} \)

- 2x previous value
- Precision indicates confidence

Within 5%
Results of the selected parameters on the individual studies

- Considerable variation across studies, particularly for \( n_I \)
- This might reflect:
  - Inter-patient differences
  - Poor mixing of interstitial fluid
  - Difficulty of the technique
  - Lack of sensitivity

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<thead>
<tr>
<th>Study</th>
<th>Study Method</th>
<th>Study Population</th>
<th>Study optimal ( n_I )</th>
<th>Study optimal ( \gamma )</th>
<th>Study min. error</th>
<th>Error at selected ( (n_I, \gamma) )</th>
</tr>
</thead>
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<tr>
<td>Jansson et al. (1993)</td>
<td>Clamp</td>
<td>Healthy non-obese</td>
<td>0.0054</td>
<td>0.30</td>
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<td>Castillo et al. (1994)</td>
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<td>0.0031</td>
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<td>0.44</td>
<td>0.044</td>
<td>0.204</td>
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<td>Sjøstrand et al. (2002)</td>
<td>Clamp</td>
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<td>Clamp</td>
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<td>0.70</td>
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<td>OGGT</td>
<td>Healthy obese</td>
<td>0.0400</td>
<td>0.46</td>
<td>0.058</td>
<td>0.516</td>
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</tbody>
</table>
Comparison of results

Comparison to literature

- Limited direct comparisons as few models use physiological compartment

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<thead>
<tr>
<th>Study</th>
<th>$n_I$</th>
<th>$Y$</th>
<th>$t_{1/2}$</th>
</tr>
</thead>
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<tr>
<td>This study</td>
<td>0.006 min$^{-1}$</td>
<td>0.5</td>
<td>58 min</td>
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<tr>
<td>Lin et al. (2010)</td>
<td>0.003 min$^{-1}$</td>
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<td>116 min</td>
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<tr>
<td>Lotz et al. (2008)</td>
<td>0.0486 min$^{-1}$</td>
<td>0.6</td>
<td>7 min</td>
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</tbody>
</table>

\[ t_{1/2} = \frac{\ln(2)}{n_I + n_C} \]

- Lin et al. $\rightarrow$ long half-life due to insulin pooling and delayed utilisation
- Lotz et al. $\rightarrow$ Parameters based on C-peptide from van Cauter et al.

- $t_{1/2}$ in the range 25-130 mins
  - Mari & Valerio 1997
  - Natali 2000
  - Turnheim & Waldhaeusl 1998
Insulin transport kinetics directly impacts SI

→ model applications

Used data from 6 published microdialysis studies to refine interstitial insulin kinetic parameters

\[ \gamma = 0.5 \]

\[ n_l = 0.006 \text{ min}^{-1} \]
Questions?