Determining the relative efficacy of a number of PID and PD models that relate insulin secretion to bolus induced glucose excursions

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Abstract: Endogenous insulin secretion ($U_N$) plays the leading role in glucose homeostasis. Understanding pathological changes in $U_N$ may enable greater insight into the etiology of metabolic disorders particularly those related to hyperglycemia. The dynamic insulin sensitivity and secretion test (DISST) is a dynamic test that is able to quantify patient-specific insulin sensitivity ($SI$) values and $U_N$ profiles. The DISST uses measured glucose, insulin and C-peptide assays with pharmaco-kinetic/dynamic glucose, insulin and C-peptide models to identify $SI$ and $U_N$ profiles. This study proposes a range of proportional-integral-derivative (PID) and proportional-derivative (PD) models to define $U_N$ as a function of glucose concentration. With relatively low percentage of residual error between measured C-peptide and fitted C-peptide response from the PID and PD models, it elucidates a more direct physiological link between insulin secretion to glucose concentration level.

1. INTRODUCTION

Insulin is secreted by pancreatic $\beta$ cells to maintain normoglycemia. Impaired endogenous insulin secretion ($U_N$) is part of major cause metabolic disorders, such as glucose intolerance or hyperglycemia. Hyperglycemia, if left untreated, ultimately leads to type 2 diabetes (T2D). Understanding the $U_N$ secretion profile is thus a critical aspect of characterizing this metabolic disorder (Ferrannini et al., 2005, Pacini et al., 2003).

Assessing insulin secretion through mathematical modelling received considerable attention during the 1970s (Bergman et al., 1971, Grodsky, 1972, Cerasti et al., 1974). Unlike insulin sensitivity ($SI$) (DeFronzo et al., 1979), there is no gold standard for $\beta$ cell function or $U_N$. However, modelling insulin secretion as a function of peripheral C-peptide levels by mathematical deconvolution has become a widespread approach (Eaton et al., 1980, Van Cauter et al., 1992). This method proves more accurate than direct measurement of insulin levels as insulin and C-peptide are co-secreted in an equimolar fashion from $\beta$ cells (Rubenstein et al., 1969) and the rate of insulin clearance is more variable than the rate of C-peptide clearance.

Relationships between insulin sensitivity and insulin secretion have been defined by previous studies (Docherty et al., Bergman et al., 1981, Bergman et al., 2002, Cretti et al., 2001, Cobelli et al., 2007). The intravenous glucose tolerance test (IVGTT) with minimal model has been the most frequently used model-based (Toffolo et al., 1999, Breda et al., 2001b). However, the minimal model is known to produce ambiguous $SI$ values and erratic correlation with the gold standard, euglycemic hyperinsulinaemic clamp (EIC) (Saad et al., 1994, Pillonetto et al., 2002). The DISST provides a highly correlated metric of $SI$ to the EIC with $R=0.81$ (McAuley et al., 2011). The DISST also provides quantitative measures of $U_N$ via deconvolution of C-peptide data (Lotz et al., 2010).

Finally, the nature of the feedback interaction between of glucose excursions and the resultant secretion of $U_N$ has received some attention in previous studies (Breda et al., 2001b). However, the aim of this study was to further validate the previously proposed proportional-derivative (PD) gain model of the glucose/$U_N$ dynamic to a proportional, integral and derivative (PID) gain model.

2. METHODOLOGY

2.1 Participants

82 female participants were recruited from the Otago region of New Zealand to take part in a 10-week dietary intervention trial defined in Te Morenga et al (2010). Inclusion criteria required a body mass index (BMI) greater than 25, or greater than 23 and a family history of type 2 diabetes, or ethnic disposition toward type 2 diabetes. Participants were excluded if they had a major illness, including established diabetes, at the time of testing. In total, 74 participants provided 200 full test DISST data sets. The cohort details were summarised and presented in Table 1.

Table 1: Participants details

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age [years]</th>
<th>BMI [kg·m⁻²]</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>M/F</td>
<td>Q1 Q2 Q3*</td>
<td>Q1 Q2 Q3*</td>
<td>NGT/ IFG/ T2DM**</td>
</tr>
<tr>
<td>-----</td>
<td>-------------</td>
<td>--------------</td>
<td>--------</td>
</tr>
<tr>
<td>0/ 74</td>
<td>35</td>
<td>27.6</td>
<td>63/ 11/0</td>
</tr>
<tr>
<td>43</td>
<td>32.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>37.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Q1 Q2 Q3 are the IQR values from tabulated data.
** NGT, normal glucose tolerance; IFG, impaired fasting glucose; T2DM, type 2 diabetes mellitus.
2.2 Clinical Procedure

Participants reported in the morning after an overnight fast. Each participant had a cannula inserted in the ante-cubital fossa (vein in inner elbow) for blood sampling and administration of glucose and insulin boluses. Blood samples were drawn at t=0, 5, 10, 15, 20, 25, 30, 35, 40 and 50 minutes. The 10g IV glucose bolus (50% dextrose and 50% normal saline) was administered intravenously at t=6 minute. The 1U IV insulin bolus was administered intravenously at t=16 minute. Blood samples were assayed for plasma glucose (Enzymatic glucose hexokinase assay, Abbot Labs, Illinois USA), insulin and C-peptide concentration (ELISA Immunoassay, Roche, Mannheim, Germany).

2.3 Physiological Model

2.3.1 DISST Model

The DISST provides quantitative measures of both SI and U_N profile (Lotz et al., 2010, McAuley et al., 2007, McAuley et al., 2011), and is similar to the insulin modified IVGTT, which uses an alternative dosage and typical modelling approach (Bergman et al., 1979, Ward et al., 2001). The DISST model identifies the U_N profile via the deconvolution of C-peptide assays (Van Cauter et al., 1992).

Equations 1-5 of DISST model is categorized by:

\[ \dot{C} = -(k_1 + k_2)C + k_2 Y + \frac{U_N}{V_p} \]  
\[ \dot{Y} = -k_1 Y + k_1 C \]  
\[ \dot{I} = -n_e I - n_i I - n_c \frac{I}{V_p} (I - Q) + \frac{U_{ex}}{V_p} \]  
\[ \dot{Q} = -(\frac{n_c + n_i}{V_q}) Q + \frac{n_i}{V_q} I \]  
\[ \dot{G} = -p_{gu}(G - G_b) - S_i(GQ - G_bQ_b) + \frac{P_t}{V_b} \]

where the nomenclature is shown in Table 2.

Typically, the DISST model uses the participants fasting glucose level (G_0) as their basal glucose concentration (G_B). However, evidence suggests that G_B and insulin concentration is slightly higher than their overnight ‘basal’ levels especially for diabetes participant (Holman et al., 1977, Holman et al., 1978, Holman et al., 1981, Holman et al., 1979). In this analysis, G_B was identified in concert with SI and V_q using the Gauss Newton parameter identification method.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unit</th>
<th>Description</th>
<th>Role</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>pmol·L(^{-1})</td>
<td>Plasma C-peptide concentration</td>
<td>measured</td>
</tr>
<tr>
<td>I</td>
<td>mU·L(^{-1})</td>
<td>Plasma insulin concentration</td>
<td>measured</td>
</tr>
<tr>
<td>G</td>
<td>mmol·L(^{-1})</td>
<td>Blood glucose concentration</td>
<td>measured</td>
</tr>
<tr>
<td>Y</td>
<td>pmol·L(^{-1})</td>
<td>Intestinal C-peptide concentration</td>
<td>simulated</td>
</tr>
<tr>
<td>Q</td>
<td>mU·L(^{-1})</td>
<td>Intestinal insulin concentration</td>
<td>simulated</td>
</tr>
<tr>
<td>U_N</td>
<td>mU·min(^{-1})</td>
<td>Endogenous insulin concentration</td>
<td>simulated/secretion</td>
</tr>
<tr>
<td>k_i, k_2, k_3</td>
<td>min(^{-1})</td>
<td>C-peptide transport rates</td>
<td>a-priori</td>
</tr>
<tr>
<td>V_p</td>
<td>L</td>
<td>Plasma insulin distribution volume</td>
<td>a-priori</td>
</tr>
<tr>
<td>V_q</td>
<td>L</td>
<td>Intestinal insulin degradation rate</td>
<td>a-priori</td>
</tr>
<tr>
<td>n_e</td>
<td>min(^{-1})</td>
<td>Basal blood glucose rate</td>
<td>a-priori</td>
</tr>
<tr>
<td>n_i</td>
<td>min(^{-1})</td>
<td>Non-insulin mediated glucose disposal rate</td>
<td>a-priori</td>
</tr>
<tr>
<td>n_c</td>
<td>min(^{-1})</td>
<td>Hepatic insulin clearance rate</td>
<td>a-priori</td>
</tr>
<tr>
<td>G_B</td>
<td>mmol·L(^{-1})</td>
<td>Basal glucose concentration</td>
<td>identified</td>
</tr>
<tr>
<td>V_g</td>
<td>L</td>
<td>Glucose distribution volume</td>
<td>identified</td>
</tr>
<tr>
<td>n_w</td>
<td>min(^{-1})</td>
<td>Interstitial C-peptide concentration</td>
<td>identified</td>
</tr>
<tr>
<td>s_1</td>
<td>1</td>
<td>Fractional first-pass hepatic insulin extraction</td>
<td>identified</td>
</tr>
<tr>
<td>SI</td>
<td>L·mU(^{-1})·min(^{-1})</td>
<td>Insulin sensitivity</td>
<td>identified</td>
</tr>
</tbody>
</table>

2.3.2 U_N model

Four U_N models are proposed in this paper. The proposed U_N models were categorized into 2 main elements; with or without U_B value, and with or without integral control, φ_1.

Model 1 - PID\(_{UB}\):

\[ U_N = U_B + \phi_p(G - G_B) + \phi_d(G) + \phi_i \int_0^t (G - G_B)\ dt + \phi_d(G) \]  

Model 2 - PD\(_{UB}\):

\[ U_N = U_B + \phi_p(G - G_B) + \phi_d(G) \]  

Model 3 - PID\(_{ambil}\):

\[ U_N = \phi_p G + \phi_i \int_0^t (G - G_B)\ dt + \phi_d(G) \]
Model 4 - PD only:

\[ U_N = \phi_P G + \phi_D \langle \dot{G} \rangle \] (9)

where \( U_N \) is the modelled endogenous insulin secretion [mU·min\(^{-1}\)]; \( U_B \) is basal insulin [mU·min\(^{-1}\)]; \( \phi_P, \phi_I \) and \( \phi_D \) are the proportional, integral and derivative gains [mU·L\(^{-1}\)·min\(^{-1}\), mU·L·min\(^{-1}\)·min\(^{-1}\) and mU·L·mmol\(^{-1}\)], respectively. \( \langle \dot{G} \rangle \) indicates the coefficient of \( \phi_D \) is equal to zero if negative.

\( U_B \) is derived from Equation 1 and 2 assuming a steady state at \( t = 0 \) minute:

\[ U_B = k_2 C_0 V_p \] (10)

where \( C_0 \) denotes a steady state C-peptide measured value at \( t = 0 \).

2.4 Parameter Identification

Experimental data was fit to the DISST model using the iterative integral method (IIM) (Docherty et al., 2012, Docherty et al., 2009). Initially, C-peptide data was deconvoluted using Equations 1-2 to define \( U_N \). The IIM was used to identify \( n_1 \) and \( x_1 \) in Equation 3 from insulin data, and \( G_B, S_I \) and \( V_p \) in Equation 5 from glucose data. Note that, \( G_B \) was identified in concert with \( S_I \) and \( V_p \) using the Gauss Newton parameter identification method. Later, \( \phi_P, \phi_I \) and \( \phi_D \) were identified using IIM with the glucose simulation of Equation 5 and measured C-peptide data. Equation 1 and \( U_N \) from Equations 6-9 can be used to define \( \dot{C} \):

\[ \dot{C} = -(k_1 + k_3)C + k_2 Y + \ldots \]
\[ \ldots + \frac{U_B + \phi_P G + \phi_I \int_0^t (G - G_B) dt + \phi_D \langle \dot{G} \rangle}{V_p} \]

Next, rearranging known parameters and PID terms, yields:

\[ V_p [\dot{C} + (k_1 + k_3)C + k_2 Y] - U_B = \phi_P G + \phi_I \int_0^t (G - G_B) dt + \phi_D \langle \dot{G} \rangle \] (12)

Integrating both side yields:

\[ \int_0^t G dt + \phi_I \int_0^t (G - G_B) dt + \phi_D \langle \dot{G} \rangle dt = \frac{\phi_P t^2}{2} + \phi_I \int_0^t (G - G_B) dt + \phi_D \langle \dot{G} \rangle t \]

\[ = V_p \left[ C_0 - C_0 + \int_0^t (k_1 + k_3)C - k_2 Y dt - U_B \int_0^t dt \right] \frac{\int_0^t (G - G_B) dt + \phi_D \langle \dot{G} \rangle}{\phi_P t} \]

\[ = V_p \frac{\int_0^t (G - G_B) dt + \phi_D \langle \dot{G} \rangle}{\phi_P t} \]

\[ = \left[ \begin{array}{c} \phi_P t^2 \frac{\int_0^t (G - G_B) dt + \phi_D \langle \dot{G} \rangle}{\phi_P t} \end{array} \right] = \left[ \begin{array}{c} \phi_P t \frac{\int_0^t (G - G_B) dt + \phi_D \langle \dot{G} \rangle}{\phi_P t} \end{array} \right] \]

\[ = \left[ \begin{array}{c} \phi_P t \frac{\int_0^t (G - G_B) dt + \phi_D \langle \dot{G} \rangle}{\phi_P t} \end{array} \right] \]

Gains of the PID models were identified using Equation 14 whereas the \( C \phi I_i \) column of the matrix was struck off for the PD models. The performances of these \( U_N \) PID and PD models were assessed via model residuals and interpretation of population trends.

2.5 Statistics and Analysis

Model residuals and interpretation of population trends were used to assess the performance of these PID and PD models based on fitted C-peptide versus measured C-peptide values. The residual error of C-peptide determines the performance of the \( U_N \) profile of PID and PD models against deconvoluted \( U_N \) profile as shown in Equation 15-17.

Mean Residual error of C-peptide (\( \mu \)) is defined:

\[ \mu(t) = \frac{1}{n} \sum_{i=1}^{n} (C_{fitted}(t) - C_{measured}(t)) \] (15)

Standard error of C-peptide (\( \sigma_c \)) is defined:

\[ \sigma_c(t) = \frac{\sigma(t)}{\sqrt{n}} \] (16)

where standard deviation (\( \sigma \)) is defined as:

\[ \sigma = \sqrt{\frac{\sum (C_{fitted}(t) - \mu(t))^2}{n}} \] (17)

The \( p \)-values are defined with signed ranksum (\( p_r \)) and Kolmogorov Smirnov test (\( p_k \)). All analysis was undertaken using MATLAB (R2013b, Mathworks, Inc., Natick, MA, USA).

3. RESULTS

Table 3 shows the identified parameter values across the cohort. There were less significant differences between derivative gains, \( \phi_P \) of Equation 6 and 7 (Signed ranksum: \( p_r<0.001 \) and Kolmogorov Smirnov: \( p_k=0.85 \)) and \( \phi_P \) of Equation 8 and 9 (\( p_r<0.001, p_k=0.92 \)). This result shows the performance of each derivative controller from each model was the same when capturing the effects of increased glucose concentrations. The same phenomenon can be seen for \( \phi_P \) for the PID only or PD only models (\( p_r<0.001, p_k=0.53 \)). However, a distinct significant difference in \( \phi_P \) for PID or PD model with \( U_B \) value (\( p_r<0.001, p_k=0.03 \)).

Fig. 1a shows the \( U_N \) profile from the proposed PID and PD models from Equation 6-9 and the deconvoluted \( U_N \) profile from Equation 1. Fig. 1b shows a typical model response fitted to the measured C-peptide data with the modelled responses of Equation 11.

Fig. 2 illustrates the residual error of all PID and PD models between the measured C-peptide data and the response modelled by Equation 11. Residual errors for PID only or PD only value tended to stay within 10% of the measured data, which is within measurement error.
Table 3: Tabulated data of basal blood glucose (GB), insulin sensitivity (SI), distribution volume of glucose (Vg) and PID gains identified across 200 participants

<table>
<thead>
<tr>
<th></th>
<th>GB [×10^{-3}]</th>
<th>SI [×10^{-3}]</th>
<th>Vg</th>
<th>PIDUB (Eq (6))</th>
<th>PIDUB (Eq (7))</th>
<th>PIDonly (Eq (8))</th>
<th>PIDonly (Eq (10))</th>
</tr>
</thead>
<tbody>
<tr>
<td>25%</td>
<td>3.37</td>
<td>4.40</td>
<td>12.30</td>
<td>7.41</td>
<td>9.93</td>
<td>7.69</td>
<td>13.11</td>
</tr>
<tr>
<td>Median</td>
<td>4.10</td>
<td>6.20</td>
<td>13.97</td>
<td>21.33</td>
<td>18.86</td>
<td>11.33</td>
<td>31.48</td>
</tr>
<tr>
<td>75%</td>
<td>4.55</td>
<td>8.52</td>
<td>15.76</td>
<td>50.66</td>
<td>39.61</td>
<td>17.32</td>
<td>61.35</td>
</tr>
</tbody>
</table>

4. DISCUSSION

The DISST protocol measures C-peptide with plasma glucose and insulin. The typical DISST approach regarding C-peptide identifies $U_N$ via a mathematical deconvolution (or direct inversion) process. However, identifying $U_N$ in such a way fails to elucidate the connection between glucose concentrations and the $U_N$ reaction. By defining the model-based $U_N$ profiles as dependent on glucose levels the modelling approach is more physiologically representative. It has been shown that insulin secretion is dependent on both peripheral glucose levels, and glucose gradient (Cherrington, 1999).

The $U_N$ PIDUB model in Equation 6 defines $U_B$ based on information from the fasted C-peptide measurement. The proportional and integral terms ($\phi_P$ and $\phi_I$) effectively determines the second phase of $U_N$ ($U_2$) and is thus, an important characteristic in the prediabetic state (Porie et al., 2012). The derivative term ($\phi_D$) determines the first phase of $U_N$ ($U_1$) as a function of increasing glucose level. This approach has been applied previously by Cobelli et al. and Ferrannini et al. (Mari et al., 2002, Dalla Man et al., 2010, Toffolo et al., 2001, Breda et al., 2001a). However, the proposed PIDUB and PDUB models offers simplicity compare to previous models. Furthermore, Cobelli et al and Ferrannini et al used kinetic models of C-peptide developed by Eaton et al. (Eaton et al., 1980); where the proposed PID and PD models use the kinetic C-peptide model from Van Cauter et al. (Van Cauter et al., 1992).

In contrast, The PIDonly and PDonly models have not been applied previously. The approach differs by assuming $U_B$ can be defined as a function of GB and $\phi_P$. As a result, $\phi_P$ takes the role of identifying the basal endogenous insulin production rate while $\phi_I$ aims to identify $U_2$. Equation 7 and 9 provided a validation of the impact of integral gains towards the identification process of $U_N$.

Fig. 1(a) shows the difference between deconvoluted $U_N$ profile and identified $U_N$ from the proposed PID and PD models. It can be clearly seen that the general trends of $U_N$ from the proposed models were in accordance with the deconvoluted $U_N$ profile. However, $U_N$ identified from the PIDonly or PDonly models were more consistent to the deconvoluted $U_N$ profile in comparison to the PIDUB or PDUB.

![Fig. 1: $U_N$ (A) and C-peptide (B) profile for Subject 108. The solid black line is the deconvoluted $U_N$ derived from Equations 1-2. The ‘+’ are C-peptide measured data points.](image1)

![Fig. 2: Residual error (mean and standard error, SE=SD/N) between the measured C-peptide data and the response modelled by Equations 6-9.](image2)
models. Fig. 1(b) shows the fitting profile of C-peptide of response model by PID or PD models and Equation 1. The C-peptide profile from response model of PIDonly and PDonly models is more accurate than the more established approaches. This result is further confirmed by the residual plot in Fig. 2.

Fig. 2 shows the residual error between measured C-peptide data and the response model by PID and PD models and Equation 1. Residual errors for PIDonly or PDonly value tended to stay within the 10% of the measured data. The residuals for the PIDonly and PDonly models were higher in comparison. However, all were within measurement errors.

Fig. 1(b) shows that the PIDonly and PDonly models capture the inflection in the C-peptide decay which is not captured by the typical approach. This difference results in much lower overall residuals that are not distant from the assay error reported by the manufacturer (CV=4.5%). Fig. 1 and 2 show minimal impact of the integral control term towards N identification. Hence, it may be a sensible recommendation that φ should be ignored in future studies.

This study was undertaken in a cohort of adult female participants that were considered ‘at-risk’ of type 2 diabetes and related metabolic disorders. Hence, the outcomes of this study may be isolated to cohorts of this type. However, it may be reasonably assumed that gender does not play a significant role in the modulation of insulin secretion as a function of glucose excursions. Furthermore, this cohort is the cohort of greatest clinical interest to the mitigation of glycemic and other metabolic disorders. Further confirmation must be undertaken in various other cohorts.

5. CONCLUSIONS

This study presented a thorough analysis of proportional-integral-derivative and proportional-derivative control models of insulin secretion. The proposed models linked insulin secretion to glucose concentration and able to deliver a good compromise between model simplicity and accuracy particularly model 4 (PDonly). This analysis found that the ideal model formulation does not require integral control, and the basal secretion rate should be located via a proportional gain and the basal glucose concentration. Although the proposed model requires further validation, it is likely to be useful for analysis of the pathogenesis of T2D as it captures the physiological determinants of patient-specific N profile.

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REFERENCES


