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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 β 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, Cerasi *et al.*, 1974). Unlike insulin sensitivity (*SI*) (DeFronzo *et al.*, 1979), there is no gold standard for β 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 β 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

Sex M/ F	Age [years] Q1 Q2 Q3*	BMI [kg·m^{-2}] Q1 Q2 Q3*	Status NGT/ IFG/ T2DM**
0/ 74	35 43 50	27.6 32.6 37.0	63/ 11/ 0

* 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 dosing 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:

C-peptide Pharmaco-Kinetics,

$$\dot{C} = -(k_1 + k_3)C + k_2 Y + \frac{U_N}{V_p} \tag{1}$$

$$\dot{Y} = -k_2 Y + k_1 C \tag{2}$$

Insulin Pharmaco-Kinetics,

$$\dot{I} = -n_k I - n_L \frac{I}{1+\alpha_I I} - \frac{n_I}{V_p}(I - Q) + \frac{U_{ex}}{V_p} + (1 - x_L)\frac{U_N}{V_p} \tag{3}$$

$$\dot{Q} = -\left(n_C + \frac{n_I}{V_q}\right)Q + \frac{n_I}{V_q} I \tag{4}$$

and Glucose-Insulin Pharmaco-Dynamics

$$\dot{G} = -p_{gu}(G - G_B) - S_I(GQ - G_B Q_B) + \frac{P_t}{V_g} \tag{5}$$

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 the G_0 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_g using the Gauss Newton parameter identification method.

Table 2: Nomenclature of the DISST model

Variable	Unit	Description	Role
C	pmol·L^{-1}	Plasma C-peptide concentration	measured
I	mU·L^{-1}	Plasma insulin concentration	measured
G	mmol·L^{-1}	Blood glucose concentration	measured
Y	pmol·L^{-1}	Interstitial C-peptide concentration	simulated
Q	mU·L^{-1}	Interstitial insulin concentration	simulated
Q_B	mU·L^{-1}	Basal interstitial insulin concentration	simulated
U_N	mU·min^{-1}	Endogenous insulin secretion	simulated/ deconvoluted
k_1, k_2, k_3	min^{-1}	C-peptide transport rates	*a-priori*
V_p	L	Plasma insulin distribution volume	*a-priori*
V_q	L	Interstitial insulin distribution volume	*a-priori*
n_k	min^{-1}	Renal insulin clearance rate	*a-priori*
n_I	min^{-1}	Plasma-interstitial diffusion rate	*a-priori*
n_C	min^{-1}	Interstitial insulin degradation rate	*a-priori*
U_{ex}	mU·min^{-1}	Exogenous insulin input rate	*a-priori*
P_t	mmol·min^{-1}	Exogenous glucose input rate	*a-priori*
p_{gu}	min^{-1}	Non-insulin mediated glucose disposal rate	*a-priori*
α_I	L·mU^{-1}	Hepatic insulin clearance saturation parameter	*a-priori*
G_B	mmol·L^{-1}	Basal blood glucose concentration	identified
V_g	L	Glucose distribution volume	identified
n_L	min^{-1}	Hepatic insulin clearance rate	identified
x_L	1	Fractional first-pass hepatic insulin extraction	identified
SI	L·mU^{-1}·min^{-1}	Insulin sensitivity	identified

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_I.

Model 1 - PID$_{UB}$:

$$U_N = U_B + \phi_P(G - G_B) + \cdots \ldots + \phi_I \int_0^t (G - G_B)dt + \phi_D\langle\dot{G}\rangle \tag{6}$$

Model 2 - PD$_{UB}$:

$$U_N = U_B + \phi_P(G - G_B) + \phi_D\langle\dot{G}\rangle \tag{7}$$

Model 3 - PID$_{only}$:

$$U_N = \phi_P G + \phi_I \int_0^t (G - G_B)dt + \phi_D\langle\dot{G}\rangle \tag{8}$$

Model 4 - PD_{only}:

$$U_N = \phi_P G + \phi_D \langle \dot{G} \rangle \tag{9}$$

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

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

$$U_B = k_3 C_0 V_p \tag{10}$$

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_L and x_L in Equation 3 from insulin data, and G_B, SI and V_g in Equation 5 from glucose data. Note that, G_B was identified in concert with SI and V_g using the Gauss Newton parameter identification method. Later, ϕ_P, ϕ_I and ϕ_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 $\dot{C}$:

$$\dot{C} = -(k_1 + k_3)C + k_2 Y + \cdots \\ \ldots + \frac{U_B + \phi_P G + \phi_I \int_0^t (G - G_B)dt + \phi_D \langle \dot{G} \rangle}{V_p} \tag{11}$$

Next, rearranging known parameters and PID terms, yields:

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

Integrating both side yields:

$$\underbrace{\phi_P \int_0^i G\, dt}_{C\phi P_i} + \underbrace{\phi_I \int_0^i (G - G_B)dt}_{C\phi I_i} + \underbrace{\phi_D \int_0^i \langle \dot{G} \rangle dt}_{C\phi D_i} \\ = \underbrace{V_p \left[C_i - C_0 + \int_0^i (k_1 + k_3)C - k_2 Y\, dt\right] - U_B \int_0^i dt}_{RHS_i} \tag{13}$$

Grouping terms and redefining in a least squares form, yields:

$$\begin{bmatrix} C\phi P_1 & C\phi I_1 & C\phi D_1 \\ \vdots & \vdots & \vdots \\ C\phi P_i & C\phi I_i & C\phi D_i \end{bmatrix} \begin{Bmatrix} \phi_P \\ \phi_I \\ \phi_D \end{Bmatrix} = \begin{bmatrix} RHS_1 \\ \vdots \\ RHS_i \end{bmatrix} \tag{14}$$

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 de-convoluted U_N profile as shown in Equation 15-17.

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

$$\mu(t) = \frac{1}{n} \sum C_{fitted}(t) - C_{measured}(t) \tag{15}$$

Standard error of C-peptide (σ_μ) is defined:

$$\sigma_\mu(t) = \frac{\sigma(t)}{\sqrt{n}} \tag{16}$$

where standard deviation (σ) is defined as:

$$\sigma = \sqrt{\frac{\sum \left(C_{fitted}(t) - \mu(t)\right)^2}{n}} \tag{17}$$

The *p*-values are defined with signed ranksum (p_{rs}) and Kolmogrov Smirnov test (p_{ks}). 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, ϕ_D of Equation 6 and 7 (Signed ranksum: p_{rs}<0.001 and Kolmogorov Smirnov: p_{ks}=0.85) and ϕ_D of Equation 8 and 9 (p_{rs}<0.001, p_{ks}=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 ϕ_P for the PID_{only} or PD_{only} models (p_{rs}<0.001, p_{ks}=0.53). However, a distinct significant difference in ϕ_P for PID or PD model with U_B value (p_{rs}<0.001, p_{ks}=0.03).

Fig. 1a the shows 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 (G_B), insulin sensitivity (SI), distribution volume of glucose (V_g) and PID gains identified across 200 participants

				PID_{UB} (Eq (6))			PD_{UB} (Eq (7))		PID_{only} (Eq (8))			PD_{only} (Eq (10))	
	G_B	SI [×10^{-4}]	V_g	ϕ_P	ϕ_I [×10^{-2}]	ϕ_D [×10^{2}]	ϕ_P	ϕ_D [×10^{2}]	ϕ_P	ϕ_I [×10^{-2}]	ϕ_D [×10^{2}]	ϕ_P	ϕ_D [×10^{2}]
25%	3.37	4.40	12.30	7.41	9.93	7.69	13.11	6.98	33.27	0.15	7.15	36.01	7.32
Median	4.10	6.20	13.97	21.33	18.86	11.33	31.48	11.40	44.19	1.05	11.57	46.56	12.01
75%	4.55	8.52	15.76	50.66	39.61	17.32	61.35	17.19	56.64	26.19	18.67	60.05	19.28

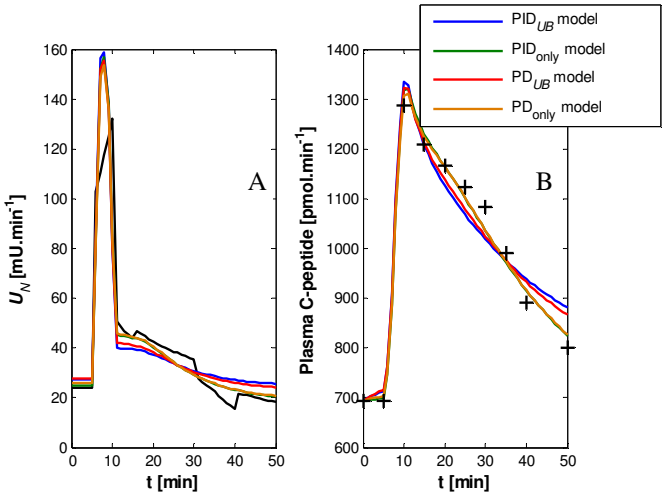

Fig. 1: U_N (A) and C-peptide (B) profile for Subject 108. The solid black line is the deconvoluted U_N derived from Equations 1-2. The '+' are C-peptide measured data points.

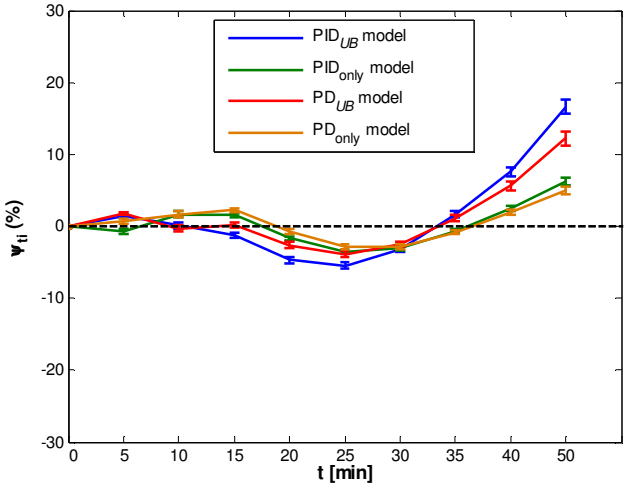

Fig. 2: Residual error (mean and standard error, SE=SD/√N) between the measured C-peptide data and the response modelled by Equations 6-9.

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 PID_{UB} model in Equation 6 defines U_B based on information from the fasted C-peptide measurement. The proportional and integral terms (ϕ_P and ϕ_I) effectively determines the second phase of U_N (U_2) and is thus, an important characteristic in the prediabetic state (Pories *et al.*, 2012). The derivative term (ϕ_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 PID_{UB} and PD_{UB} 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 PID_{only} and PD_{only} models have not been applied previously. The approach differs by assuming U_B can be defined as a function of G_B and ϕ_P. As a result, ϕ_P takes the role of identifying the basal endogenous insulin production rate while ϕ_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 PID_{only} or PD_{only} models were more consistent to the deconvoluted U_N profile in comparison to the PID_{UB} or PD_{UB}

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 PID_{only} and PD_{only} 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 modelled by PID and PD models and Equation 1. Residual errors for PID_{only} or PD_{only} value tended to stay within the 10% of the measured data. The residuals for the PID_{UB} and PD_{UB} models were higher in comparison. However, all were within measurement errors.

Fig. 1(b) shows that the PID_{only} and PD_{only} 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 U_N identification. Hence, it may be a sensible recommendation that ϕ_I 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 (PD_{only}). 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 U_N profile.

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