A Proportional-Derivative Endogenous Insulin Secretion model with an Adapted Gauss Newton Approach

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Abstract: Endogenous insulin (U_N) secreted by pancreatic β-cells plays a leading role in glucose homeostasis. Pathological changes in U_N can enable early diagnosis of metabolic dysfunction before the emergence of type 2 diabetes. The dynamic insulin sensitivity and secretion test (DISST) is a dynamic test that is able to quantify participant-specific insulin sensitivity (*SI*) values and U_N profiles. Like most studies, the DISST uses direct inversion of C-peptide concentration measurements to quantify a U_N profile which relies on the assumption that insulin and C-peptide are equimolarly secreted from β-cells. This study develops a proportional-derivative (PD) control model that defines U_N as a function of glucose concentration to provide further insight and modeling capability for this prediabetic state. Results show that individuals with normal glucose tolerance (NGT) tend to have higher gain ratio compared to individuals with impaired fasting glucose (IFG) with median values of 19.11 and 2.79 min, respectively. In particular, the main difference between the U_N profiles of NGT and IFG group lies within the derivative gain (ϕ_D), specifically in first phase secretion (U_1). A higher value of ϕ_D is needed in response to an abrupt increase in plasma glucose level. This proposed model offers model simplicity as well as a link between insulin secretion and glucose concentration that is able to provide more information in determining each participant's glycemic condition.

Keywords: Type 2 diabetes, Endogenous insulin secretion, Parameter identification, Insulin sensitivity, Closed-loop feedback-control system.

1. INTRODUCTION

Although the pathogenesis of type 2 diabetes (T2D) varies across individuals, typical pathogenesis includes the failure of the pancreatic β-cell to compensate for insulin resistance (IR) and the glucose load (Breda *et al.* 2002; Ferrannini 1997; Kahn 1998; Mari *et al.* 2002). The inability of β-cells to produce enough insulin to clear excess glucose results in high glucose concentrations in the blood. However, this elevation in blood glucose (BG) does not occur until insulin demand exceeds the maximal insulin secretion rate in the much later stages of the pathogenesis of type 2 diabetes, well after initial pathological changes in endogenous insulin secretion (U_N) have occurred (Ferrannini 1997; Pories and Dohm 2012).

Measuring endogenous insulin secretion may thus enable early diagnosis of metabolic dysfunction long before elevated BG occurs. Many studies have been conducted to determine the best technique for identifying endogenous insulin secretion (U_N) by directly associating the insulin secretion with insulin sensitivity (Albareda *et al.* 2000; Bergman *et al.* 2002; Lotz *et al.* 2010; McAuley *et al.* 2007). The gold standard, Euglycemic hyper-insulinaemic Clamp (EIC) (Defronzo *et al.* 1979) provides insulin sensitivity ($SI = IR^{-1}$) by quantifying the glucose necessary to compensate for an increased insulin level by maintaining glucose concentration at a normal fasting concentration (typically ~4.6 mmol·L^{-1}) (McAuley *et al.* 2001). However, the EIC does not provide U_N characteristics and may thus miss early dysfunction.

Unlike *SI*, there is no gold standard for β cell function or U_N. Most secretion studies use deconvolution of C-peptide concentration measurements to identify the U_N profile (Eaton *et al.* 1980; Polonsky *et al.* 1986; Van Cauter *et al.* 1992). This method is accurate because insulin and C-peptide are co-secreted in an equimolar fashion from β cells (Rubenstein *et al.* 1969). However, accuracy can be compromised by low sampling frequency. In addition, insulin undergoes a substantial first pass hepatic extraction before reaching the peripheral circulation, which affects the ability to precisely predict U_N directly from insulin measurements (Hovorka and Jones 1994; Polonsky and Rubenstein 1986). Thus, empirical or model-based methods that use C-peptide have proven a better means of U_N quantification (Pacini and Mari 2003).

The dynamic insulin sensitivity and secretion test (DISST) quantifies a patient-specific *SI* value and U_N profile. The DISST *SI* value is highly correlated to the EIC ($R_{pearson}$ = 0.81), and the test can contrast U_N characteristics across patient groups with different levels of *IR* (McAuley *et al.* 2011). The DISST defines the patient-specific U_N based on deconvolution of measured C-peptide data. However, these measurements are often relatively sparse. Hence, while

diagnostically effective, there remains scope to reduce the sampling rate, and thus invasiveness and cost.

Regulation of blood glucose by U_N is effectively controlled by a closed-loop feedback-control system (Cherrington 1999). Proportional-derivative (PD) control models have previously been proposed to link the defined patient-specific U_N profile to glucose excursions. However, the main objective of this study is to further expand on the accuracy of this previously proposed PD control U_N model in identifying and discriminating the U_N profile for normal glucose tolerance (NGT) and impaired fasting glucose (IFG) participants in the presence of reduced data.

2. METHODOLOGY

2.1 Participants and Data

A total of 94 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). The median participant age was 42.5 years (IQR 34.5 – 50.5) and the median BMI was 32.34 kg/m^2 (27.9 – 36.94) Inclusion criteria required a body mass index (BMI) greater than 25, or greater than 23 and a family history of T2D, or ethnic disposition toward T2D. Participants were excluded if they had a major illness, including established diabetes, at the time of testing. In total, 68 participants provided 204 full test DISST data sets at week 0, week 4 and week 10 of the intervention.

2.2 Clinical Procedure

Participants reported in the morning after at least 10 hours of overnight fasting. 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. A 10g IV glucose bolus (50% dextrose and 50% normal saline) was administered at t=6 minutes. 1U of IV insulin bolus was administered at t=16 minutes. 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 model provides quantitative measures of both *SI* and U_N profile (Lotz *et al.* 2010; McAuley *et al.* 2011; McAuley *et al.* 2007), and was derived, in part, from the Minimal model of glucose dynamics (Bergman *et al.* 1979). The DISST model identifies the U_N profile via the deconvolution of C-peptide assays (Van Cauter *et al.* 1992). The DISST model is defined:

C-peptide Pharmaco-Kinetics:

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

$$\dot{Y} = -k_2 Y + k_1 C \quad (2)$$

Insulin Pharmaco-Kinetics:

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

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

and Glucose-Insulin Pharmaco-Dynamics:

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

where equation nomenclature is shown in Table 1.

Table 1. 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	L·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 PD U_N model

Regulation of blood glucose by insulin secretion is controlled by a physiological feedback-control system (Cherrington 1999). Hence, a PD U_N model was proposed to estimate U_N as a function of increasing glucose (derivative control, ϕ_D) and glucose above basal (proportional control, ϕ_P). Since IV glucose is reasonably evenly distributed in blood plasma over 10-15 minutes, time delays were not modelled in the coefficients of ϕ_D or ϕ_P.

$$U_N = U_B + \phi_P(G - G_B) + \phi_D\langle\dot{G}\rangle \quad (6)$$

where U_N is the modelled endogenous insulin secretion [mU·min^{-1}]; U_B is basal insulin [mU·min^{-1}]; ϕ_P and ϕ_D are the proportional, and derivative gains [mU·L·mmol^{-1}·min^{-1} and mU·L·mmol^{-1}, respectively]. Note that $\langle \dot{G} \rangle$ indicates the coefficient of ϕ_D is equal to zero if negative. U_B is derived from Equations 1 and 2, assuming a steady state at t = 0 minute:

$$U_B = k_3 C_0 V_p \tag{7}$$

where C_0 denotes steady state C-peptide measured value at $t = 0$.

2.4 Parameter Identification

Initially, most of the *a-priori* parameters are quantified as functions of the participant anatomical characteristics (weight, height, sex, age) defined by Van Cauter *et al.* (Van Cauter *et al.* 1992). Typically, the DISST methodology sets p_{gu} as a constant of 0.004 min^{-1} (Lotz *et al.* 2010).

A seven parameter identification approach adapting the Gauss Newton method is developed to define the participant-specific parameters of G_B, SI, V_G, ϕ_P, ϕ_D, n_L and x_L. The iterative function is defined:

$$\mathbf{x}_{i+1} = \mathbf{x}_i - (\mathbf{J}^{\mathbf{T}}\mathbf{J})^{-1}\mathbf{J}^{\mathbf{T}}\boldsymbol{\psi} \tag{8}$$

and minimises $\|\boldsymbol{\psi}\|_2$.

where $\mathbf{x}_i = [G_B, SI_i, V_{Gi}, \phi_{Di}, \phi_{Pi}, n_{Li}, x_{Li}]$ and i is the iteration number. The Jacobian matrix (**J**) and the residual matrix ($\boldsymbol{\psi}$) are defined:

$$\mathbf{J}(\mathbf{x}_i) = \begin{bmatrix} \frac{\delta\psi_1}{\delta G_B} & \frac{\delta\psi_1}{\delta SI} & \cdots & \frac{\delta\psi_1}{\delta x_L} \\ \frac{\delta\psi_2}{\delta G_B} & \frac{\delta\psi_2}{\delta SI} & \cdots & \frac{\delta\psi_2}{\delta x_L} \\ \vdots & \vdots & \ddots & \vdots \\ \frac{\delta\psi_n}{\delta G_B} & \frac{\delta\psi_n}{\delta SI} & \cdots & \frac{\delta\psi_n}{\delta x_L} \end{bmatrix} \tag{8a}$$

$$\boldsymbol{\psi}(\mathbf{x}_i) = \begin{bmatrix} (G(x_i,t_1) - G_{M,1})/\overline{G_M} \\ \vdots \\ (G(x_i,t_n) - G_{M,n})/\overline{G_M} \\ (C(x_i,t_1) - C_{M,1})/\overline{C_M} \\ \vdots \\ (C(x_i,t_n) - C_{M,n})/\overline{C_M} \\ (I(x_i,t_1) - I_{M,1})/\overline{I_M} \\ \vdots \\ (I(x_i,t_n) - I_{M,n})/\overline{I_M} \end{bmatrix} \tag{8b}$$

where $I(\mathbf{x}_i,t_s)$, $G(\mathbf{x}_i,t_s)$ and $C(\mathbf{x}_i,t_s)$ are the simulated values at $t = t_s$ given $\mathbf{x}_i$; $I_{M,s}$, $G_{M,s}$ and $C_{M,s}$ are the measured values at $t = t_s$ (s=1..n); n is the number of measured samples; $\overline{I_M}$, $\overline{G_M}$ and $\overline{C_M}$ are the mean measured values of each measured species.

To avoid model misidentification issues, insulin samples taken within 10 minutes of insulin administration and glucose samples taken within 10 minutes of glucose injection were ignored in the model fit to minimize errors introduced by variable effects of intravascular mixing (Caumo *et al.* 1999; Edsberg *et al.* 1987; Lotz 2007). V_G is constrained within the range of 0.12Bw to 0.25Bw where bodyweight (Bw) is measured in kg and the coefficients have units of L·kg^{-1} (Defronzo *et al.* 1979; Ferrannini and Mari 1998; Lotz 2007; Lotz *et al.* 2010).

2.5 Statistics and Analysis

In this study, the PD U_N model accuracy was assessed via the produced residual matrix ($\boldsymbol{\psi}$). The results of ϕ_P and ϕ_D are reported in median and interquartile range (IQR) for 3 patient categories: All, NGT, and IFG. All analyses were undertaken using MATLAB (R2013b, Mathworks, Inc., Natick, MA, USA).

3. RESULTS

Fig. 1 shows the simulated versus measured plasma insulin, glucose, C-peptide and U_N profiles from one participant. Note again that the insulin and glucose samples taken within 10 minutes of bolus injection were ignored due to unmodelled mixing effects. In general, using the DISST model with a PD U_N model and a Gauss Newton identification method shows that the simulated data fits relatively very well against the measured data.

Among 204 full DISST test data sets, 17 were classed as IFG based on a cut-off value of 5.56 mmol·L^{-1} (100 mg·dL^{-1} (ADA 2012)) of fasting glucose (G_0). Fig. 2 shows the distribution of ϕ_D/ϕ_P ratio against G_0 across NGT and IFG group sets of data. It also shows that the median value of ϕ_D/ϕ_P for NGT is higher than for IFG with 19.11 min and 2.76 min, respectively.

Fig. 3 shows the gain distribution of ϕ_D versus ϕ_P across both groups. It clearly shows that ϕ_D generates greater value than ϕ_P. A statistical summary of both gains are presented in Table 2 with ranksum and Kolmogorov-Smirnov significance values.

Table 2. Summary statistics of derivative (ϕ_D) and proportional (ϕ_P) gains.

	Median [IQR]		
Group	ϕ_P	ϕ_D	$\frac{\phi_D}{\phi_P}$
NGT	69.58 [43.06, 96.41]	1283.4 [879.4, 1848.1]	19.11 [13.2, 27.6]
IFG	69.47 [49.5, 100.1]	302.55 [25.72, 756.46]	2.79 [0.15, 13.25]
$p_{ranksum}$	0.75	<0.0001	<0.0001
p_{ks}	0.78	<0.0001	<0.0001

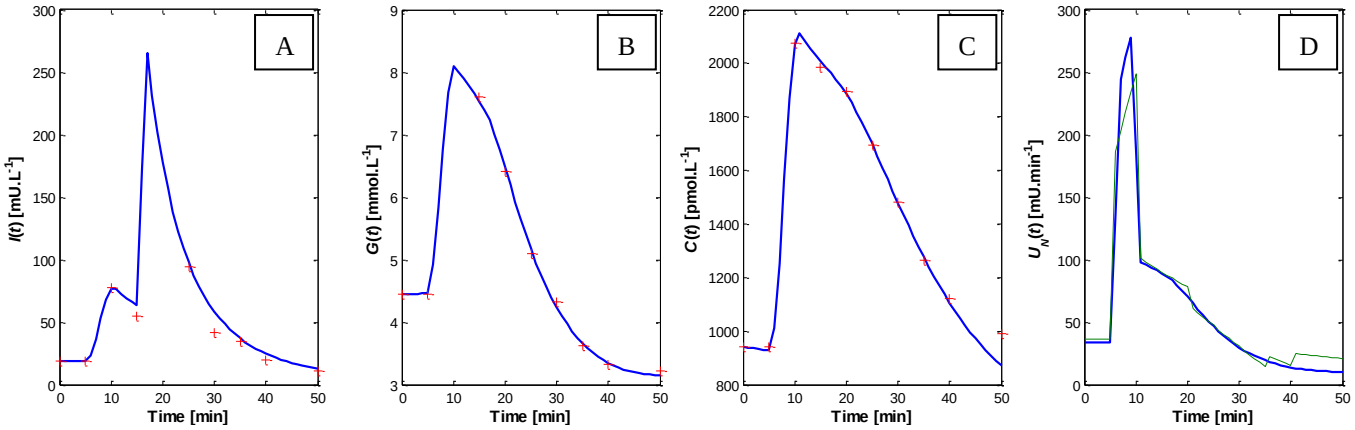

Fig. 1: Simulated (solid blue line) and measured (red '+' symbol) of; (A) plasma insulin, (B) glucose and (C) C-peptide for a typical participant response to the DISST model. (D) Endogenous insulin secretion profile identified from PD U_N model (solid blue line) and from deconvoluted C-peptide measurement (solid green line).

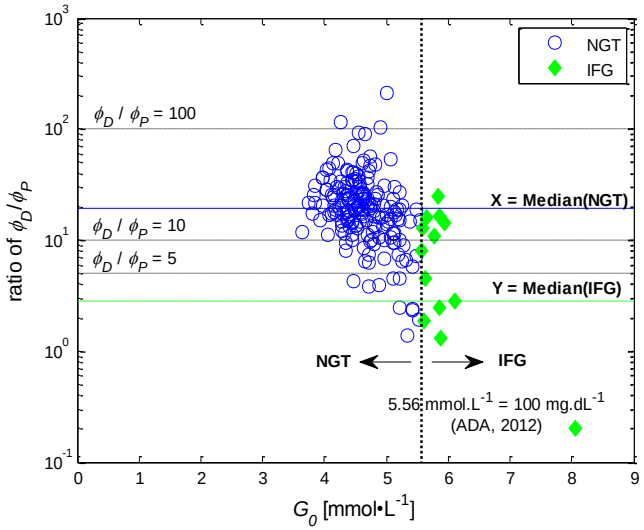

Fig. 2: Distribution of ϕ_D/ϕ_P against G_0 where X = 19.11 min and Y = 2.79 min.

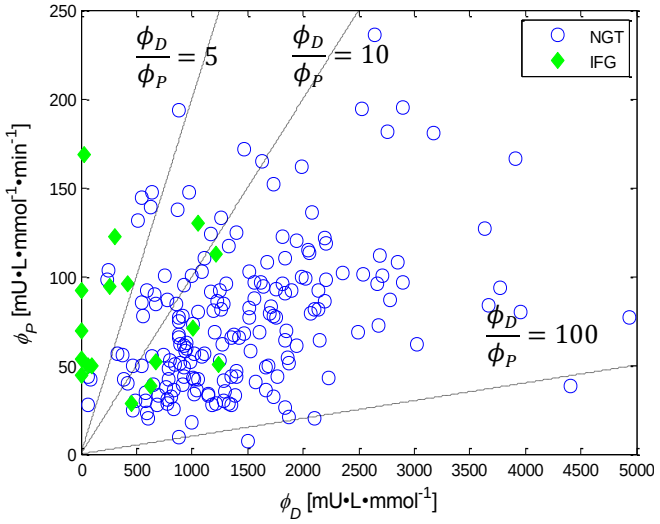

Fig. 3: Distribution of ϕ_D over ϕ_P during the intervention study. The ϕ_D/ϕ_P = 5, 10, and 100 dotted lines are shown for context.

4. DISCUSSION

The DISST validation study used deconvolution of C-peptide data to determine participant specific U_N profiles (McAuley *et al.* 2011). However, regulation of blood glucose concentrations is effectively a closed-loop feedback-control system (Cherrington 1999). Hence, a proportional-derivative (PD) model is used that directly mimics this behaviour to identify a smoother, more physiological, U_N profile. The main purpose of this study was to validate the PD U_N model in differentiating NGT and IFG participants.

The proposed PD U_N model distinguishes U_N profile into 3 major roles; basal endogenous insulin secretion (U_B), first phase insulin secretion and second phase insulin secretion. The derivative term (ϕ_D) determines the first phase of U_N (U_1) based on the dependence of insulin secretion on the positive rate of change of glucose concentration. The proportional term (ϕ_P) effectively determines the second phase of U_N (U_2) based on a proportional function over the basal glucose concentration at steady state level.

Fig. 1 depicts the difference between identified U_N from the PD U_N model and the deconvoluted U_N profile. It shows that the general trends of U_N from the proposed PD U_N model were in accordance with the deconvolved U_N profile. Moreover, the proposed PD U_N model provides a direct physiological link between glucose concentration and resultant insulin secretion, which is physiologically more accurate and provides a means to model this behaviour with limited data. Hence, the main benefit of the proposed model may be found when a lack of resolution in the C-peptide samples reduces accuracy of deconvolved U_N profiles.

Fig. 2 shows the distribution of ϕ_D/ϕ_P against fasting glucose (G_0) on a log scale with the ADA guideline. It can be seen that the NGT group has higher gain ratio compared to IFG group where the median value of gain ratio was ~7× higher. Only 5 out of 187 NGT results are below the IFG median value showing clear separation. Theoretically, an individual with higher insulin resistance will have a limited first phase secretion, causing a much lower ϕ_D/ϕ_P ratio than a healthy participant with a high first phase insulin secretion.

Hence, the resultant difference in median ratios is somewhat expected across the NGT and IFG group.

The pathogenesis of T2D progresses through 3 distinct stages: 1) normal glucose tolerance (NGT); 2) IFG and impaired glucose tolerance (IGT); and 3) T2D (Pories and Dohm 2012). IFG and IGT represent an intermediate metabolic state between normal glucose homeostasis and diabetes (Alberti and Zimmet 1998; Nathan *et al.* 2007). In general, determining the value of the derivative gain (ϕ_D) and proportional gain (ϕ_P) is crucial when assessing which stage the participant belongs to. Studies have shown that loss of first phase insulin secretion is an independent predictor of type 2 diabetes (Bunt *et al.* 2007; Del Prato and Tiengo 2001; Pratley and Weyer 2001; Vranic *et al.* 1971; Weyer *et al.* 1999). In addition, second phase insulin secretion is an important characteristic in the prediabetic state (McAuley *et al.* 2011; Pories and Dohm 2012). In the model presented in the present study, this would be evident in a reduction in the value of ϕ_D. Table 2 shows that ϕ_D was significantly lower in the IFG subgroup of the cohort. Hence, the findings of this study are in agreement with previous studies.

Fig. 3 shows that while ϕ_D gains are scattered across a wider range from ~0 to 4.93×10^3 mU·L·mmol^{-1}, ϕ_P remains at narrow range from 7.09 to 236.06 mU·L·mmol^{-1}·min^{-1}. In addition, Table 2 shows that although ϕ_P hold almost identical value across both group, ϕ_D remains significantly different between the NGT and IFG groups. Thus, it can be said that as ϕ_D decreases, the metabolic state moves from NGT toward the first known symptoms of diabetes. Fig. 3 also shows this context with lines of ϕ_D/ϕ_P ratio discriminating different patient types for the most part.

Hypothetically, while both gains play an important role in defining the participant-specific U_N profile, it clearly shows that the comparatively important derivative gain, (ϕ_D) appears to be more important in defining the metabolic state of the participant. Clinically, *IR* participants relied more heavily on the second phase or proportional gain in maintaining the glucose homeostasis. This latter point was inferred by the diagnostic value of U_2 in McAuley *et al.* (2011), and matches clinical expectations (Ferrannini 1997).

If ϕ_P is fixed to a certain value, ϕ_D will vary when quantifying the participant-specific U_N profile depending on the metabolic state of the participant. A value of $\phi_D \approx 0$ is predicted for participants with type 2 diabetes. Furthermore, down sampling measured glucose data when assessing U_N characteristics over a limited period of time from 0 to 30 min will result in significantly reduced clinical cost and clinical attention during the trial. With fewer samples, the outcome result would provide less effective information compared to a full data set. However, further validation is needed to prove both assumptions and to determine the degree to which the findings of this study can be interpolated in a down-sampling exercise.

While this PD control U_N model requires further validation, it is likely to be useful for analysis of the pathogenesis of T2D as it captures the physiological determinants of participant-specific U_N profiles. This model provides a direct physiological link between insulin secretion to glucose concentration as well as insulin sensitivity.

5. CONCLUSIONS

This study presented a thorough analysis of proportional-derivative model of insulin secretion adapting a Gauss Newton parameter identification method. The proposed model offers model simplicity as well as a link between insulin secretion and glucose concentration. In addition, it provides more information in determining the condition stage of each participant.

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