

# 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  $\beta$ -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  $\beta$ -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 ( $\phi_D$ ), specifically in first phase secretion ( $U_1$ ). A higher value of  $\phi_D$  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.*

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## 1. INTRODUCTION

Although the pathogenesis of type 2 diabetes (T2D) varies across individuals, typical pathogenesis includes the failure of the pancreatic  $\beta$ -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  $\beta$ -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  $\sim 4.6 \text{ mmol}\cdot\text{L}^{-1}$ )

(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  $\beta$  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  $\beta$  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 ( $R_{\text{pearson}} = 0.81$ ), 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<sup>2</sup> (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 Pharmacokinetics:*

$$\dot{C} = -(k_1 + k_3)C + k_2Y + \frac{U_N}{v_p} \quad (1)$$

$$\dot{Y} = -k_2Y + k_1C \quad (2)$$

*Insulin Pharmacokinetics:*

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

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

*and Glucose-Insulin Pharmacodynamics:*

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

where equation nomenclature is shown in Table 1.

Table 1. Nomenclature of the DISST model

Variable	Unit	Description	Role
$C$	pmol·L <sup>-1</sup>	Plasma C-peptide concentration	measured
$I$	mU·L <sup>-1</sup>	Plasma insulin concentration	measured
$G$	mmol·L <sup>-1</sup>	Blood glucose concentration	measured
$Y$	pmol·L <sup>-1</sup>	Interstitial C-peptide concentration	simulated
$Q$	mU·L <sup>-1</sup>	Interstitial insulin concentration	simulated
$Q_B$	mU·L <sup>-1</sup>	Basal interstitial insulin concentration	simulated
$U_N$	mU·min <sup>-1</sup>	Endogenous insulin secretion	simulated/ deconvoluted
$k_1, k_2, k_3$	min <sup>-1</sup>	C-peptide transport rates	<i>a-priori</i>
$v_p$	L	Plasma insulin distribution volume	<i>a-priori</i>
$v_q$	L	Interstitial insulin distribution volume	<i>a-priori</i>
$n_k$	min <sup>-1</sup>	Renal insulin clearance rate	<i>a-priori</i>
$n_I$	L·min <sup>-1</sup>	Plasma-interstitial diffusion rate	<i>a-priori</i>
$n_C$	min <sup>-1</sup>	Interstitial insulin degradation rate	<i>a-priori</i>
$U_{ex}$	mU·min <sup>-1</sup>	Exogenous insulin input rate	<i>a-priori</i>
$P_t$	mmol·min <sup>-1</sup>	Exogenous glucose input rate	<i>a-priori</i>
$p_{gu}$	min <sup>-1</sup>	Non-insulin mediated glucose disposal rate	<i>a-priori</i>
$\alpha_I$	L·mU <sup>-1</sup>	Hepatic insulin clearance saturation parameter	<i>a-priori</i>
$G_B$	mmol·L <sup>-1</sup>	Basal blood glucose concentration	identified
$v_g$	L	Glucose distribution volume	identified
$n_L$	min <sup>-1</sup>	Hepatic insulin clearance rate	identified
$x_L$	1	Fractional first-pass hepatic insulin extraction	identified
$SI$	L·mU <sup>-1</sup> ·min <sup>-1</sup>	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,  $\phi_D$ ) and glucose above basal (proportional control,  $\phi_P$ ). Since IV glucose is reasonably evenly distributed in blood plasma over 10-15 minutes, time delays were not modelled in the coefficients of  $\phi_D$  or  $\phi_P$ .

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

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

$$U_B = k_3 C_0 V_p \quad (7)$$

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  $0.004 \text{ min}^{-1}$  (Lotz *et al.* 2010).

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

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

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

where  $\mathbf{x}_i = [G_B, SI, V_G, \phi_D, \phi_P, n_L, x_L]$  and  $i$  is the iteration number. The Jacobian matrix ( $\mathbf{J}$ ) and the residual matrix ( $\boldsymbol{\Psi}$ ) are defined:

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

$$\boldsymbol{\Psi}(\mathbf{x}_i) = \begin{bmatrix} (G(x_i, t_1) - G_{M,1})/\bar{G}_M \\ \vdots \\ (G(x_i, t_n) - G_{M,n})/\bar{G}_M \\ (C(x_i, t_1) - C_{M,1})/\bar{C}_M \\ \vdots \\ (C(x_i, t_n) - C_{M,n})/\bar{C}_M \\ (I(x_i, t_1) - I_{M,1})/\bar{I}_M \\ \vdots \\ (I(x_i, t_n) - I_{M,n})/\bar{I}_M \end{bmatrix} \quad (8b)$$

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;  $\bar{I}_M$ ,  $\bar{G}_M$  and  $\bar{C}_M$  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  $\text{L}\cdot\text{kg}^{-1}$  (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  $\phi_P$  and  $\phi_D$  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  $5.56 \text{ mmol}\cdot\text{L}^{-1}$  ( $100 \text{ mg}\cdot\text{dL}^{-1}$  (ADA 2012)) of fasting glucose ( $G_0$ ). Fig. 2 shows the distribution of  $\phi_D/\phi_P$  ratio against  $G_0$  across NGT and IFG group sets of data. It also shows that the median value of  $\phi_D/\phi_P$  for NGT is higher than for IFG with 19.11 min and 2.76 min, respectively.

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

**Table 2. Summary statistics of derivative ( $\phi_D$ ) and proportional ( $\phi_P$ ) gains.**

Group	Median [IQR]		
	$\phi_P$	$\phi_D$	$\frac{\phi_D}{\phi_P}$
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 <sub>ranksum</sub>	0.75	<0.0001	<0.0001
p <sub>ks</sub>	0.78	<0.0001	<0.0001

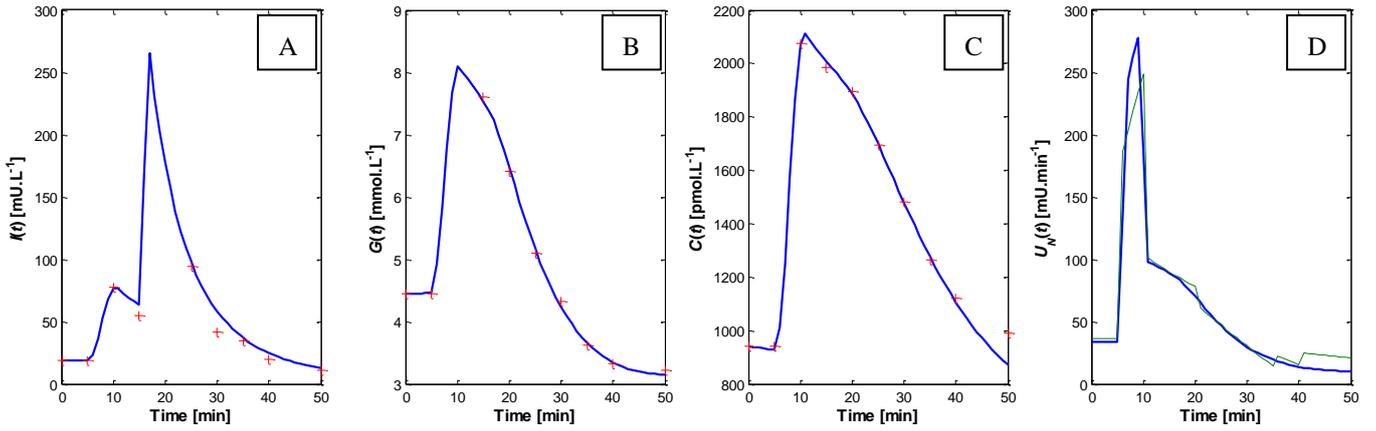


Fig. 1: Simulated (solid blue line) and measured (red '+' symbol) of; (A) plasma insulin, (B) glucose and (C) C-peptide for a typical participant response to the DISST model. (D) Endogenous insulin secretion profile identified from PD  $U_N$  model (solid blue line) and from deconvoluted C-peptide measurement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

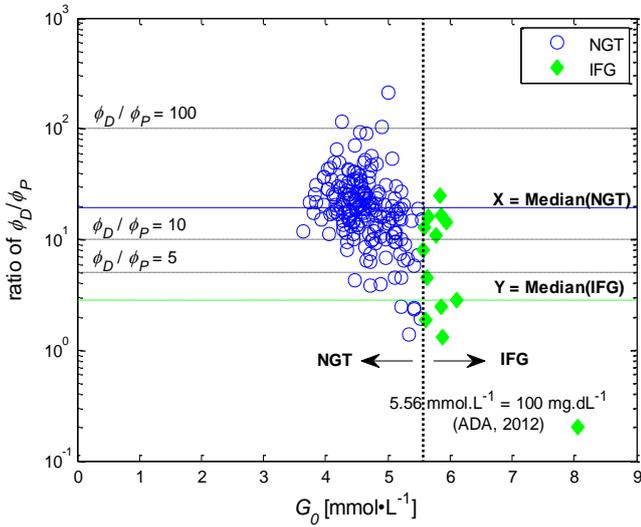


Fig. 2: Distribution of  $\phi_D/\phi_P$  against  $G_0$  where  $X = 19.11$  min and  $Y = 2.79$  min.

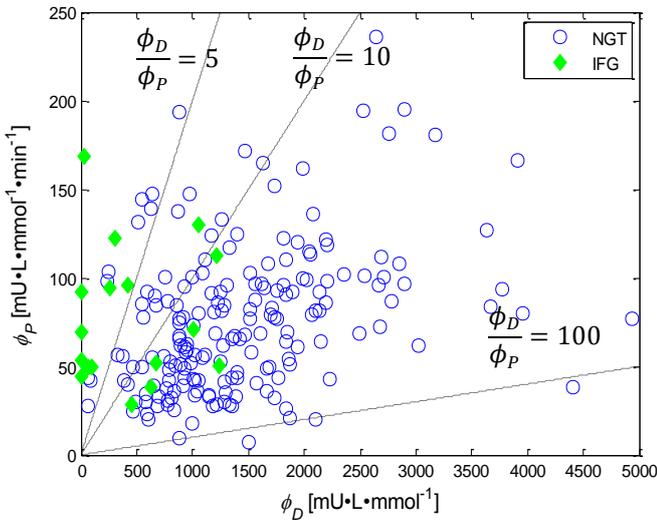


Fig. 3: Distribution of  $\phi_D$  over  $\phi_P$  during the intervention study. The  $\phi_D/\phi_P = 5, 10,$  and  $100$  dotted lines are shown for context.

#### 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 ( $\phi_D$ ) 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 ( $\phi_P$ ) 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 deconvoluted  $U_N$  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 deconvoluted  $U_N$  profiles.

Fig. 2 shows the distribution of  $\phi_D/\phi_P$  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  $\sim 7\times$  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  $\phi_D/\phi_P$  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 ( $\phi_D$ ) and proportional gain ( $\phi_P$ ) 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  $\phi_D$ . Table 2 shows that  $\phi_D$  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  $\phi_D$  gains are scattered across a wider range from  $\sim 0$  to  $4.93 \times 10^3$  mU·L·mmol<sup>-1</sup>,  $\phi_P$  remains at narrow range from 7.09 to 236.06 mU·L·mmol<sup>-1</sup>·min<sup>-1</sup>. In addition, Table 2 shows that although  $\phi_P$  hold almost identical value across both group,  $\phi_D$  remains significantly different between the NGT and IFG groups. Thus, it can be said that as  $\phi_D$  decreases, the metabolic state moves from NGT toward the first known symptoms of diabetes. Fig. 3 also shows this context with lines of  $\phi_D/\phi_P$  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, ( $\phi_D$ ) 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  $\phi_P$  is fixed to a certain value,  $\phi_D$  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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## REFERENCES

- ADA (2012) Diagnosis and classification of diabetes mellitus, *Diabetes Care*, 35 Suppl 1(S64-71)
- Albareda M., Rodriguez-Espinosa J., Murugo M., de Leiva A., Corcoy R. (2000) Assessment of insulin sensitivity and beta-cell function from measurements in the fasting state and during an oral glucose tolerance test, *Diabetologia*, 43(12), 1507-1511
- Alberti K.G., Zimmet P.Z. (1998) Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation, *Diabet Med*, 15(7), 539-553
- Bergman R., Ider Y., Bowden C., Cobelli C. (1979) Quantitative estimation of insulin sensitivity, *Am J Physiol*, 236(E667 - 677)
- Bergman R.N., Finegood D.T., Kahn S.E. (2002) The evolution of beta-cell dysfunction and insulin resistance in type 2 diabetes, *Eur J Clin Invest*, 32 Suppl 3(35-45)
- Breda E., Toffolo G., Polonsky K.S., Cobelli C. (2002) Insulin release in impaired glucose tolerance: oral minimal model predicts normal sensitivity to glucose but defective response times, *Diabetes*, 51 Suppl 1(S227-233)
- Bunt J.C., Krakoff J., Ortega E., Knowler W.C., Bogardus C. (2007) Acute insulin response is an independent predictor of type 2 diabetes mellitus in individuals with both normal fasting and 2-h plasma glucose concentrations, *Diabetes-Metabolism Research and Reviews*, 23(4), 304-310
- Caumo A., Vicini P., Zachwieja J.J., Avogaro A., Yarasheski K., Bier D.M., Cobelli C. (1999) Undermodeling affects minimal model indexes: insights from a two-compartment model, *Am J Physiol*, 276(6 Pt 1), E1171-1193
- Cherrington A.D. (1999) Banting Lecture 1997. Control of glucose uptake and release by the liver in vivo, *Diabetes*, 48(5), 1198-1214

- DeFronzo R.A., Tobin J.D., Andres R. (1979) Glucose Clamp Technique - Method for Quantifying Insulin-Secretion and Resistance, *American Journal of Physiology*, 237(3), E214-E223
- Del Prato S., Tiengo A. (2001) The importance of first-phase insulin secretion: implications for the therapy of type 2 diabetes mellitus, *Diabetes-Metabolism Research and Reviews*, 17(3), 164-174
- Eaton R.P., Allen R.C., Schade D.S., Erickson K.M., Standefer J. (1980) Prehepatic Insulin Production in Man - Kinetic-Analysis Using Peripheral Connecting Peptide Behavior, *Journal of Clinical Endocrinology & Metabolism*, 51(3), 520-528
- Edsberg B., Herly D., Hildebrandt P., Kuhl C. (1987) Insulin bolus given by sprinkler needle: effect on absorption and glycaemic response to a meal, *Br Med J (Clin Res Ed)*, 294(6584), 1373-1376
- Ferrannini E. (1997) Insulin resistance is central to the burden of diabetes, *Diabetes Metab Rev*, 13(2), 81-86
- Ferrannini E., Mari A. (1998) How to measure insulin sensitivity, *Journal of Hypertension*, 16(7), 895-906
- Hovorka R., Jones R.H. (1994) How to Measure Insulin-Secretion, *Diabetes-Metabolism Reviews*, 10(2), 91-117
- Kahn B.B. (1998) Type 2 diabetes: when insulin secretion fails to compensate for insulin resistance, *Cell*, 92(5), 593-596
- Lotz T.F.: High resolution clinical model-based assessment of insulin sensitivity. In *Department of Mechanical Engineering*, University of Canterbury, New Zealand, 2007
- Lotz T.F., Chase J.G., McAuley K.A., Shaw G.M., Docherty P.D., Berkeley J.E., Williams S.M., Hann C.E., Mann J.I. (2010) Design and Clinical Pilot Testing of the Model-Based Dynamic Insulin Sensitivity and Secretion Test (DISST), *J Diabetes Sci Technol*, 4(6), 1408-1423
- Mari A., Tura A., Gastaldelli A., Ferrannini E. (2002) Assessing insulin secretion by modeling in multiple-meal tests: role of potentiation, *Diabetes*, 51 Suppl 1(S221-226
- McAuley K.A., Berkeley J.E., Docherty P.D., Lotz T.F., Morenga L.A.T., Shaw G.M., Williams S.M., Chase J.G., Mann J.I. (2011) The dynamic insulin sensitivity and secretion test-a novel measure of insulin sensitivity, *Metabolism-Clinical and Experimental*, 60(12), 1748-1756
- McAuley K.A., Mann J.I., Chase J.G., Lotz T.F., Shaw G.M. (2007) Point: HOMA - Satisfactory for the Time Being: HOMA: the best bet for the simple determination of insulin sensitivity, until something better comes along, *Diabetes Care*, 30(9), 2411-2413
- McAuley K.A., Williams S.M., Mann J.I., Walker R.J., Lewis-Barned N.J., Temple L.A., Duncan A.W. (2001) Diagnosing insulin resistance in the general population, *Diabetes Care*, 24(3), 460-464
- Morenga L.T., Williams S., Brown R., Mann J. (2010) Effect of a relatively high-protein, high-fiber diet on body composition and metabolic risk factors in overweight women, *Eur J Clin Nutr*, 64(11), 1323-1331
- Nathan D.M., Davidson M.B., DeFronzo R.A., Heine R.J., Henry R.R., Pratley R., Zinman B. (2007) Impaired fasting glucose and impaired glucose tolerance - Implications for care, *Diabetes Care*, 30(3), 753-759
- Pacini G., Mari A. (2003) Methods for clinical assessment of insulin sensitivity and beta-cell function, *Best Pract Res Clin Endocrinol Metab*, 17(3), 305-322
- Polonsky K., Rubenstein A. (1986) Current approaches to measurement of insulin secretion, *Diabetes Metab Rev*, 2(3-4), 315-329
- Polonsky K.S., Liciniopaixao J., Given B.D., Pugh W., Rue P., Galloway J., Karrison T., Frank B. (1986) Use of Biosynthetic Human C-Peptide in the Measurement of Insulin-Secretion Rates in Normal Volunteers and Type-I Diabetic-Patients, *Journal of Clinical Investigation*, 77(1), 98-105
- Pories W.J., Dohm G.L. (2012) Diabetes: Have We Got It All Wrong?: Hyperinsulinism as the culprit: surgery provides the evidence, *Diabetes Care*, 35(12), 2438-2442
- Pratley R.E., Weyer C. (2001) The role of impaired early insulin secretion in the pathogenesis of Type II diabetes mellitus, *Diabetologia*, 44(8), 929-945
- Rubenstein A.H., Clark J.L., Malani F., Steiner D.F. (1969) Secretion of Proinsulin C-Peptide by Pancreatic Beta Cells and Its Circulation in Blood, *Nature*, 224(5220), 697-&
- Van Cauter E., Mestrez F., Sturis J., Polonsky K.S. (1992) Estimation of insulin secretion rates from C-peptide levels. Comparison of individual and standard kinetic parameters for C-peptide clearance, *Diabetes*, 41(3), 368-377
- Vranic M., Fono P., Kovacevi.N, Lin B.J. (1971) Glucose Kinetics and Fatty Acids in Dogs on Matched Insulin Infusion after Glucose Load, *Metabolism-Clinical and Experimental*, 20(10), 954-&
- Weyer C., Bogardus C., Mott D.M., Pratley R.E. (1999) The natural history of insulin secretory dysfunction and insulin resistance in the pathogenesis of type 2 diabetes mellitus, *Journal of Clinical Investigation*, 104(6), 787-794