Improving Minimal Model Identifiability in Insulin Resistant Patients Utilizing Insight from the Graphical Structural Model Identifiability Method

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The Minimal Model is often used to characterize participant responses to glucose by fitting model simulations to measured data. Although the model has met significant success defining test responses of normo-glucose tolerant (NGT) participants, the model has experienced practical identifiability issues with insulin resistant (IR) individuals.

A previous investigation of practical model identifiability hypothesized that Minimal Model identifiability of IR individuals would be improved if a bolus impulse response was followed by a sustained period of mild hypoglycemia. In this investigation, an *in-silico* Monte Carlo analysis is undertaken to observe the effect of incorporating a clamp-like period to the end of an intravenous glucose tolerance test (IVGTT-EIC) protocol. N=100 virtual patient responses to the IVGTT-EIC and frequently sampled IVGTT (FS-IVGTT) protocols are defined. Minimal Model parameter values are identified for each test includeing measurement error M=500 times. The robustness of model parameters from the two protocols is assessed via paired coefficient of variation (CV).

The CV values for the Minimal Model parameters derived from the proposed IVGTT-EIC protocol were significantly lower than the CV values from the FS-IVGTT. In particular, median CV(%) for Minimal Model parameters S_G, p_2, p_3 and V_G derived from IVGTT-EIC data was: 3.8%, 16.8%, 8.7% and 2.2%, respectively, compared to 9.3%, 43.0%, 36.0% and 2.9% respectively for the FS-IVGTT.

Minimal Model simulation of FS-IVGTT data is a well established method of measuring insulin sensitivity. However, the proposed IVGTT-EIC protocol significantly improved the identifiability of the Minimal Model over the FS-IVGTT. The success of the proposed protocol validates the utility of the graphical structural model identifiability analysis for defining robust clinical protocols.

Insulin sensitivity, Minimal Model, Structural identifiability, pharmaco-dynamics, Monte Carlo analysis, Botnia clamp.

1. INTRODUCTION

The Minimal Model is a well known representation of the fundamental insulin/glucose pharmaco dynamics (Bergman et al. 1979; Bergman et al. 1981; Caumo and Cobelli 1993; Cobelli et al. 1986). The model has successfully characterized responses to the frequently sampled intravenous glucose tolerance test (FS-IVGTT). However, it has experienced issues when applied without Bayesian methods certain cases. Notably, the model suffers practical identifiability issues when fit to dynamic test results of insulin resistant (IR) participants (Caumo et al. 1999; Cobelli et al. 1999; Pillonetto et al. 2003; Pillonetto et al. 2002; Quon et al. 1994). The model is defined:

$$\dot{G} = -S_G(G - G_0) - XG + \frac{P_X}{V_G} \quad 1$$

$$\dot{X} = p_3(I - I_0) - p_2 X \quad 2$$

$$S_I = \frac{p_3}{p_2} \quad 3$$

where: G is the plasma glucose [mmol·L-1], I is the measured insulin [mU·L-1], X is the insulin action [min^{-1}], P_X is the exogenous input, V_G is the glucose distribution volume [L], the subscript '0' denotes the basal concentrations, and S_G (glucose sensitivity) [min^{-1}], S_I (insulin sensitivity) [$L \cdot mU^{-1} \cdot min^{-1}$], p_2 [min^{-1}] and p_3 [$L \cdot mU^{-1} \cdot min^{-2}$] characterize the participant response.

Docherty *et al.* hypothesized that the reduced identifiability of the Minimal Model was due to the reduced distinction in the parameter roles in model simulation for IR participants (Docherty et al. 2011). In particular, the G-G_0 term in Equation 1 would often become negative in the later stages of the test for normo-glucose tolerant (NGT) participants, but would seldom become negative for IR patients. This result occurred because IR participants often failed to return to basal glucose concentrations at the end of a test. Thus, the

integral of the S_G coefficient (G-G_0) would show a curve over time for NGT participants, but be relatively linear for IR participants. The co-efficient of X (G) must always be positive. Hence, the integral always increases over time and is relatively similar between IR and NGT participants. Thus, it was concluded that the previously observed reduction in Minimal Model identifiability in IR participants was due to the increased distinction between the integrals of the coefficients of X and S_G in NGT participants.

Docherty *et al.* hypothesized that a potential remedy for this impaired identifiability was to include a period of mild hypoglycemia (plasma glucose ~ 4 mmol.L^{-1}) at the end of each IVGTT test (Docherty et al. 2011). It was suspected that this would increase the curvature of the integral of G-G_0. This effect could be achieved via a hyper-physiological insulin infusion with feedback glucose control similar to the hyperinsulinaemic clamp (EIC). This research evaluates such a protocol (denoted IVGTT-EIC) *in-silico* using a Monte Carlo methodology.

2. METHODOLOGY

An *in-silico* Monte Carlo analysis is done to measure the effects of altering a typical FS-IVGTT protocol on Minimal Model parameter robustness. The steps of the Monte Carlo analysis are defined:

1. Define 100 virtual participant parameter sets using previously published ranges (Bergman et al. 1981).
2. Simulate an FS-IVGTT response and an IVGTT-EIC response for each virtual participant
3. Sample each *in-silico* test responses and add assay error 500 times.
4. Identify the model parameters in each test response. Thus, 50000 parameter identification processes are undertaken for each protocol.
5. Measure the intra-participant identified parameter robustness with coefficients of variation (CV). A comparison of the coefficients of variation across the two tests is made.

2.1 Test protocols

Both the FS-IVGTT and the IVGTT-EIC use a 20g glucose bolus administered at t = 0 minutes. Both protocols will be sampled at 5-minutes intervals between t = -10 and 180 minutes and both tests will measure glucose and insulin levels in each sample. The IVGTT-EIC will differ from the FS-IVGTT by the administration of an 80 mU/min infusion of insulin between t = 61 and 180 minutes. Glycaemic control is used during the IVGTT-EIC to maintain the participants glucose level at 4 mmol·L^{-1}. The FS-IVGTT does not involve glycaemic control. Figure 1 shows a model simulation of a virtual IR participant's response to the FS-IVGTT and IVGTT-EIC protocols.

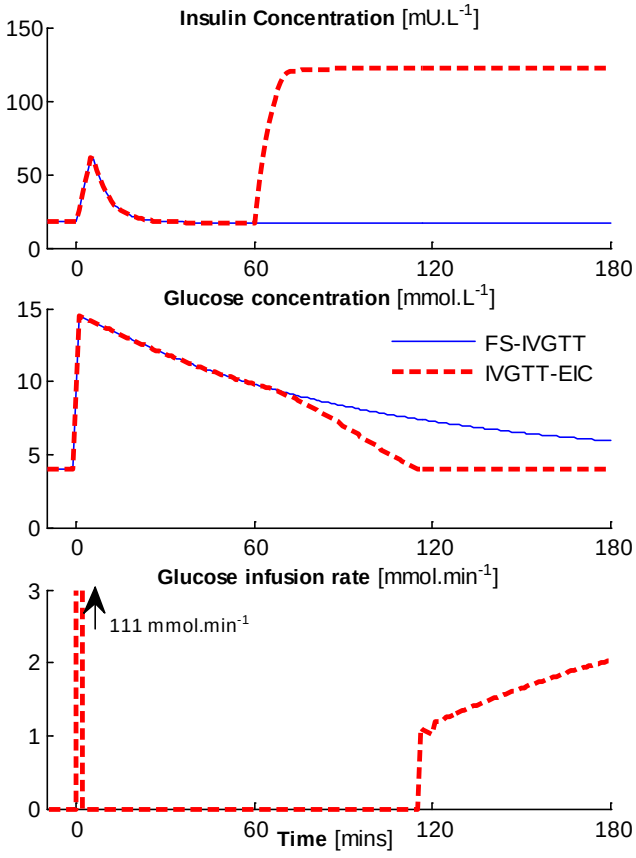

Figure 1. A typical IR participant response to the FS-IVGTT and the IVGTT-EIC protocols

2.2 Virtual patient responses

Participant characteristics were defined within ranges identified by Bergman *et al.* (Bergman et al. 1981). In this analysis, parameter values were purposefully skewed towards IR and used the distributions and relationships defined in Equations 4-7.

$$S_G = 0.005\mathrm{e}^{2.306\mathbf{R}(0,1)} \quad (4)$$

$$p_2 = 0.0025e^{3.689\mathbf{R}(0,1)} \quad (5)$$

$$p_3 = p_2(0.0001 + 0.001\mathbf{R}(0,1))\mathbf{N}(1,0.2) \quad (6)$$

$$V_G = 9 + 6\mathbf{R}(0,1) \quad (7)$$

where: $\mathbf{R}(x_1,x_2)$ is a randomly generated value on the evenly distributed range (x_1, x_2) and $\mathbf{N}(\mu,\sigma)$ is a randomly generated value with a mean μ and standard deviation of σ.

Each virtual participant response incorporated a stepwise endogenous insulin secretion response (U_N) comprising of a pre-bolus basal period, a first phase and a second phase. The basal period was defined between t = -10 and 0 and had the post hepatic value 2+$\mathbf{R}$(0,2) mU.L^{-1}.min^{-1} The first phase response was defined between t = 0 and 5 and had the post-

hepatic value of 15+**R**(0,15) mU.L^{-1}.min^{-1} (Lotz et al. 2010; Lotz et al. 2009; McAuley et al. 2011). The second phase test response was defined as 2+**R**(0,3) mU.L^{-1}.min^{-1} and was sustained until the end of the FS-IVGTT protocol or ten minutes after the insulin infusion of the IVGTT-EIC protocol (Argoud et al. 1987; Liljenquist et al. 1978).

The insulin response to the test stimulus was defined:

$$\dot{I} = -nI + U_N + \frac{U_X}{V_P} \quad 8$$

where: n is the clearance rate of insulin [min^{-1}], U_N is the endogenous insulin production [mU.L^{-1}.min^{-1}], U_X is the rate of exogenous insulin infusion [mU.min-1] and V_P is the insulin distribution volume [L]. V_P, n, I_0 and G_0 are defined:

$$V_P = \frac{V_G}{2}\mathbf{N}(1, 0.1) \quad 9$$

$$n = 0.14 + 0.04\mathbf{R}(0,1) \quad 10$$

$$I_0 = \frac{U_{N,0}}{n} \quad 11$$

$$G_0 = \mathbf{R}(4,5) \quad 12$$

The participant's I, X and G responses to the test responses were defined with the analytical solutions to the model equations (Equations 1, 2 and 8), defined:

$$I(t) = e^{-\int_0^t n dt}\left[I_0 + \int_0^t e^{\int_0^t n dt}\left(U_N + \frac{U_X}{V_P}\right)dt\right] \quad 13$$

$$X(t) = p_3 e^{-\int_0^t p_2 dt}\int_0^t e^{\int_0^t p_2 dt}\left(I(t) - I_0\right)dt \quad 14$$

$$G(t) = e^{-\int_0^t S_G + X(t) dt}\left[G_0 + \int_0^t e^{\int_0^t S_G + X(t) dt}\left(S_G G_0 + \frac{P_X(t)}{V_G}\right)dt\right] \quad 15$$

The time-variant value of $P_X(t)$ that is required for feedback glucose control in the IVGTT-EIC is calculated using an iterative method. The virtual patient response to the IVGTT-EIC protocol is simulated with Equations 13 – 15 and no feedback control. Equation 16 is then used to update the $P_X(t)$ profile between the first minute when the glucose concentration goes below 4 mmol·L^{-1} and the end of the clinical protocol (τ):

$$P_X(\tau) = \max(0, S_G(G(\tau) - G_0) + X(\tau)G(\tau))V_G \quad 16$$

where:

$$\tau = t(G < 4, \text{first})...180 \quad 17$$

Equations 15 and 16 are iterated until $G(t=180) > 3.98$mmol.L^{-1}. This methodology for finding $P_X(t)$ is possible *in-silico* but would not be possible clinically. Hence this feedback control mechanism is only possible *in silico*.

2.3 Test response sampling and Minimal Model evaluation

The glucose and insulin responses from each virtual participant is 'sampled' at 5 minute intervals from t = -10 to t = 180 minutes. This yields a total of 39 glucose and insulin data points from each participant, for each protocol. The minute-wise $P_X(t)$ profile from the IVGTT-EIC is recorded for each virtual participant.

Thirty-nine values were drawn from the distribution **N**(1, 0.02). The noise free glucose 'samples' were multiplied by these values to mimic measurement error. Likewise 39 values were drawn from the distribution **N**(1, 0.04) were multiplied with the insulin 'samples' to produce a noisy insulin data set. The same 'noise' was multiplied with both the FS-IVGTT and IVGTT-EIC data to provide 'paired' noise across the protocols.

Minimal Model parameters were identified using the MATLAB^{TM} Levenberg-Marquardt (Levenberg 1944; Marquardt 1963) parameter identification program, lsqnonlin.m with default settings and the noisy insulin and glucose data sets. $I(t)$ was defined as a linear interpolation of the noisy I data. The Levenberg-Marquardt method minimized squared error between the measured G data and the modeled simulation by optimizing the parameter set [S_G, p_2, p_3, V_G].

After 500 Monte Carlo runs with different measurement errors, the coefficient of variation (CV, standard deviation divided by mean) in each parameter for each of the 100 participant data sets is calculated for each protocol. The efficacy of the proposed IVGTT-EIC protocol will be assessed by the CV values of the model parameters. If the CV values of the IVGTT-EIC are significantly lower than those of the FS-IVGTT it may be concluded that the additional hyper-insulinaemic period enhanced the Minimal Model identifiability.

3. RESULTS

Table 1 summarizes the outcomes of the paired noise Monte Carlo experiment. The CV values of the Minimal Model parameters identified via the proposed IVGTT-EIC protocol were significantly lower than the CV values derived via a standard FS-IVGTT protocol ($p<<0.00001$ for all model parameters according to the Wilcoxon ranksum and Kolmogorov-Smirnov tests).

Note that S_G and V_G were comparatively robust to measurement error. The CV of S_I was less than the CV of its constituent parameters (p_2 and p_3). This result implies that the SI metric is slightly more robust to the susceptibility of p_2 and p_3 to measurement noise.

Table 1. Coefficients of variation (%) for the Minimal Model parameters identified from a standard FS-IVGTT and the proposed IVGTT-EIC

	FS-IVGTT			*IVGTT-EIC*		
	Q_1	**Q_2**	Q_3	Q_1	**Q_2**	Q_3
S_G	5.4	**9.3**	16.0	2.8	**3.8**	6.4
p_2	32.2	**43.0**	51.9	10.6	**16.8**	39.3
p_3	25.9	**36.0**	42.8	7.3	**8.7**	13.4
V_G	2.3	**2.9**	3.3	1.9	**2.2**	2.8
S_I	11.4	**25.0**	42.0	4.1	**8.2**	28.8

Figure 2 shows a direct comparison of the CV values for the model parameters identified with the two protocols and the cumulative distribution of CV. As the investigation used 'paired' measurement error a direct comparison is possible. The cumulative distribution curve intersections with the quartile lines are presented in Table 1.

Figure 3 shows the distribution of S_G and S_I CV values as a function of their parent values. A log-relationship was used to define the regression lines as log(CV) residuals were relatively evenly distributed. Note that the predominant improvement in parameter stability was achieved by the IVGTT-EIC protocol for the IR range of participants.

4. DISCUSSION

This investigation shows that a period of sustained, mild hypoglycemia at the end of an IVGTT protocol can improve Minimal Model identifiability. Docherty *et al.* showed a similar outcome with a comparatively simplistic model (Docherty et al. 2011) and predicted this outcome for the Minimal Model. In particular, Figure 3 shows that the most significant improvement in CV values was found for the IR participants. These results further validate the original hypothesis.

The Monte Carlo investigation enabled the application of equal noise to the model responses of both protocols. Thus, the evaluation of the model parameter robustness could be paired and the protocol comparison is more direct. Figure 2 shows that the proposed method provides more robust values in terms of V_G and p_3 for each case and in the other parameters in the significant proportion of cases.

The proposed IVGTT-EIC protocol is very clinically intensive and would be arduous to undertake and perform. However, when reasonable Minimal Model parameter values are desired, protocols of greater duration are often undertaken, albeit with a reduced sampling rate in the later stages of the test. The sampling rate of the proposed IVGTT-EIC is not reducible as a relatively frequent sampling is required for feedback control of the EIC portion of the test.

The Botnia clamp (Tripathy et al. 2003) uses a similar clinical protocol to the proposed IVGTT-EIC and is used to characterize both first phase insulin secretion and insulin sensitivity. The initial dynamic period of the Botnia clamp is used to assess insulin secretion while the clamp period is used to measure insulin sensitivity. This protocol is distinct from the proposed protocol as euglycaemia is the clamp target rather than mild hypoglycemia (~4mmol·L^{-1}). With

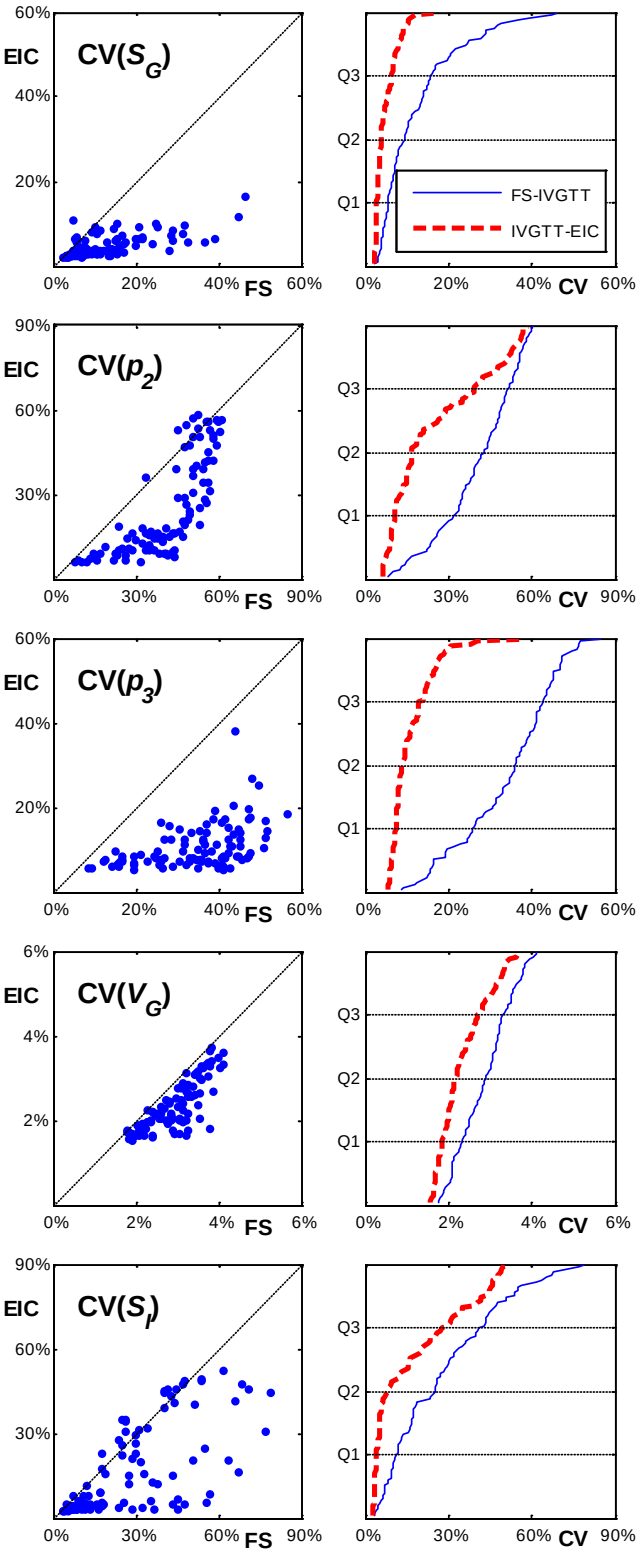

Figure 2. Coefficients of variation from the established FS-IVGTT and the proposed IVGTT-EIC protocols (n = 100) (1:1 line and quartiles dotted)

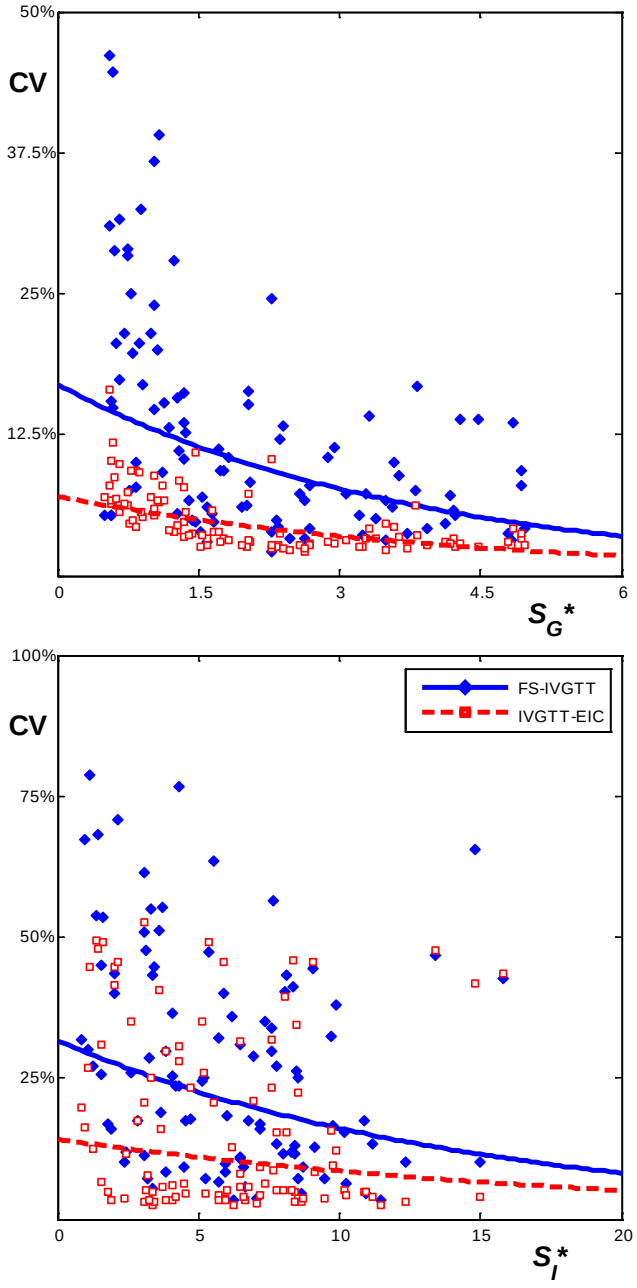

Figure 3. CV as a function of the parent values of S_G (top) and S_I (bottom) (* units of S_G $\times 10^{-2}$ min^{-1}, units of S_I $\times 10^{-4}$ $L \cdot mU^{-1} \cdot min^{-1}$)

respect to model identifiability, euglycaemia may not produce the dynamics necessary to improve model identifiability. In particular, there will be no downward curve in the integral of the S_G coefficient that is required to improve Minimal Model identifiability. Thus, according the hypothesis, the period of mild hypoglycemia is required to improve minimal model identifiability.

The validity of the outcomes of this analysis must be interpreted with recognition of the *in-silico* nature of the analysis. The virtual patients were defined with parameter values ranges that were clinically derived (ref Bergman 1980) (Bergman et al. 1981). Equation 6 defined p_3 as a vague function of p_2 to ensure a reasonable range of S_I values. This equation was derived as a best-guess estimate. Some studies have found a relationship between S_G and S_I (Cobelli et al. 1999; Erichsen et al. 2004), and a relationship between V_G and S_I may be inferred by obesity effects on S_I (Ahrén and Pacini 2005; Bergman et al. 1981). This investigation used no such relationships for lack of exact data. Thus, if a closer S_G-S_I relation exists in actual participants, the inter-parameter tradeoff could increase the CV values measured in this analysis. However, the relative CV values across the FS-IVGTT and IVGTT-EIC protocols would not likely change, with the IVGTT-EIC still providing the more stable results.

The glycaemic control period of the IVGTT-EIC was modeled idealistically, and this degree of control might not be possible in a clinical setting. In clinical practice, maintaining reasonable glucose levels via discrete glucose measurements is difficult. In the proposed protocol, the glucose must be reduced from a mild hyperglycemic state to a mild hypoglycemic state, and then maintained stable. Even achieving a reasonable level of control in such conditions would be difficult. This concern is purely clinical and would be very difficult to assess *in-silico*. Furthermore, the effect of imperfect glucose stability on parameter robustness has not yet been investigated.

The findings of this analysis imply that a clinical pilot of the proposed protocol is potentially warranted. However, it would be very difficult to assess the robustness of the model parameters without repeating the protocol. Furthermore, confirming the comparative robustness of the FS-IVGTT and IVGTT-EIC would require multiple tests. Hence, direct clinical validation would be very expensive and clinically burdensome to undertake. In contrast, a less statistically conclusive study design may involve single IVGTT-EIC tests with a reduced incidence of S_I=0 in IR participants considered a positive outcome.

5. CONCLUSIONS

Overall, this analysis confirms the predictions of the integral based model identifiability methodology and demonstrates the methods ability to define clinical protocols that produce robust model estimates. The IVGTT-EIC protocol was proposed using the identifiability method to increase Minimal Model parameter robustness for IR participants.

While the proposed protocol demonstrated a definite improvement in Minimal Model parameter robustness over an established FS-IVGTT protocol, the clinical application of the protocol may be difficult. In particular, the protocol requires a period of mild hypoglycemia, which may be difficult to achieve with feedback control based on discrete glucose measurements.

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