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Optimal Designs for Model-Based Assessment of Insulin Sensitivity and Glucose Effectiveness

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Abstract

The integrated minimal model allows assessment of clinical diagnosis indices, for example, insulin sensitivity (S_I) and glucose effectiveness (S_G), from data of the insulin-modified intravenous glucose tolerance test (IVGTT), which is laborious with an intense sampling schedule, up to 32 samples. The aim of this study was to propose a more informative, although less laborious, IVGTT design to be used for model-based assessment of S_I and S_G. The IVGTT design was optimized simultaneously for all design variables: glucose and insulin infusion doses, time of glucose dose and start of insulin infusion, insulin infusion duration, sampling times, and number of samples. Design efficiency was used to compare among different designs. The simultaneously optimized designs showed a profound higher efficiency than both standard rich (32 samples) and sparse (10 samples) designs. The optimized designs, after removing replicate sample times, were 1.9 and 7.1 times more efficient than the standard rich and sparse designs, respectively. After including practical aspects of the designs, for example, sufficient duration between samples and avoidance of prolonged hypoglycemia, we propose 2 practical designs with fewer sampling times and lower input of glucose and insulin than standard designs, constrained to prevent hypoglycemia. The optimized practical rich design is equally efficient in assessing S_I and S_G as the rich standard design, but with half the number of the samples, while the optimized practical sparse design has 1 less sample and requires 4.6 times fewer individuals for equal certainty when assessing S_I and S_G than the sparse standard design.

Keywords

glucose effectiveness, insulin sensitivity, minimal model, nonlinear mixed effects, optimal design

Diabetes mellitus is one of the major global epidemics. Its prevalence among adults over 18 years is 8.5% worldwide with type 2 diabetes (T2DM) being the most common.[1] Previously, T2DM was referred to as age-related diabetes, as its incidence increases with age, but now T2DM is increasingly occurring also at lower ages.[2] Disease state can be assessed by metabolic indices, for example, insulin sensitivity (S_I), glucose effectiveness (S_G), β-cell function, and glycosylated hemoglobin (HbA_{1C}). Euglycemic clamp is the gold standard technique for assessing S_I.[3] This procedure is labor intensive; hence, it is not used for routine analysis. An alternative method is model-based estimation of S_I using the glucose minimal model[4] with data from an intravenous glucose tolerance test (IVGTT). The IVGTTs are less labor intensive than euglycemic clamps, but still highly invasive. The standard IVGTT design includes 32 samples during 4 hours. Optimal design theory[5] has previously been used by Cobelli and Ruggeri[6] to reduce the number of samples in an IVGTT, with maintained certainty of parameters estimates in the minimal model. However, these optimizations did not include other design aspects, for example, time and size of glucose dose. In addition, optimizations were performed for the glucose minimal model, conditioned on insulin observations and thus simultaneous optimization of design aspects related to insulin was impossible, as well as optimization for patients with T2DM. The reduced sampling schedule from Cobelli and Ruggeri included 14 samples; that design was later evaluated using both the standard two-stage method and the iterative two-stage population approach.[7]

An integrated minimal model of glucose and insulin was recently developed[8] that combines the labeled glucose 2-compartment minimal model[9] and insulin

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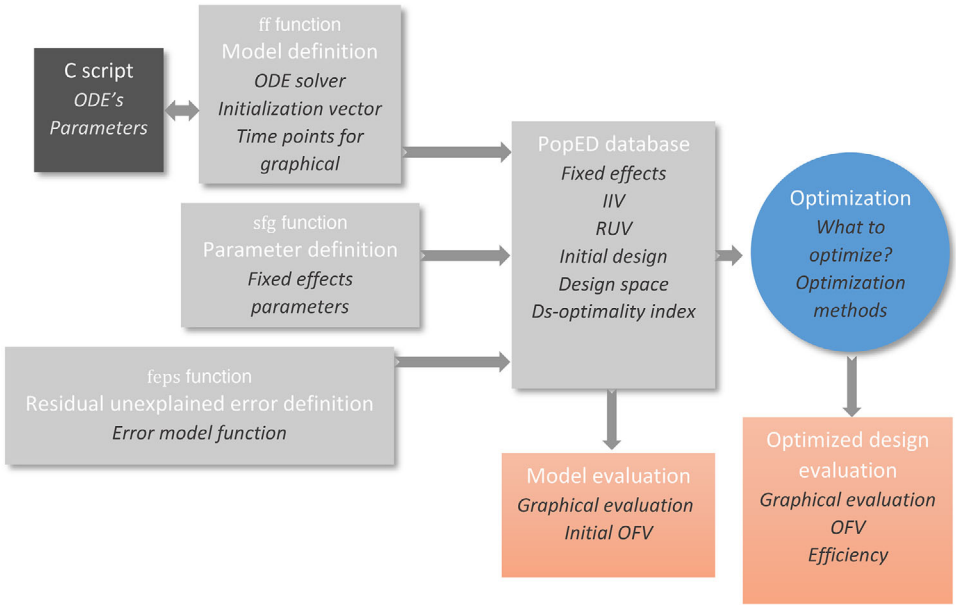

Figure 1. A schematic representation of the PopED optimization tool, as it was used for optimizing the integrated minimal model. The gray boxes represent functions that are used in PopED, listing the content that is defined within each function. The black box represents the C compilation of the ordinary differential equations. The red boxes represent evaluation functions for initial or optimized study designs, and the blue circle represents the optimization function in PopED.

minimal model,[10] with new functions for feedback of glucose on endogenous glucose production. The integrated minimal model provides a mechanistic portrait of glucose-insulin system, in addition to the clinical assessment of metabolic indices. The model has full simulation capabilities that allow its use in drug development for dose selection or for exploration of disease and drug effects on indices or key sites of action in the glucose-insulin system. Furthermore, the model can be used to optimize the study design of clinical trials or diagnosis, enabling a simplified study design, while maintaining or even increasing information content. The objective of this study was to propose an improved study design of IVGTT in patients with T2DM, using the integrated minimal model with D_S-optimality criteria for S_I and S_G, optimizing the design for number of samples, doses and times of the glucose and insulin infusion as well as sampling times.

Material and Methods

This study aimed to find the most informative design of the IVGTT regarding S_I and glucose effectiveness, while at the same time making the design clinically useful. The optimal design approach does not consider clinically important aspects, for example, risk of hypoglycemia; thus, this study shows how to change the design and optimize the certainty of S_I and S_G, measured as optimal design efficiency, while maintaining a low risk of hypoglycemia, for example, glucose concentrations <58 mg/dL in a maximum of 5% of patients at any glucose measurement.

Optimal Design

An optimal design in the current setting is a design that gives the highest certainty of the parameters estimates of a model. In D_S-optimal design, parameters that are more important to estimate precisely can be prioritized so that the resulting design is optimal for estimating these important parameters, sometimes with a design that is unfavorable for other parameters in the model. In this work, the metabolic indices, S_G and S_I, were the focus for optimization. Our optimization was performed in optimal design R package PopED.[11,12] More details on optimal design theory and PopED settings can be found in the Appendix S1 and the workflow is depicted in Figure 1.

To compare the improvement between competing optimized designs of a given reference design, efficiency is calculated as the ratio of objective function values (OFVs), between the optimized design and the references design, raised to a power of the reciprocal of the number of important parameters:

$$\text{Efficiency} = \left(\frac{\text{OFV}_{\text{optimized design}}}{\text{OFV}_{\text{reference design}}}\right)^{1/\text{Np}} \quad (1)$$

The OFV is a measurement of the expected precision of the design and efficiency measures the proportion of individuals needed with the reference design to achieve

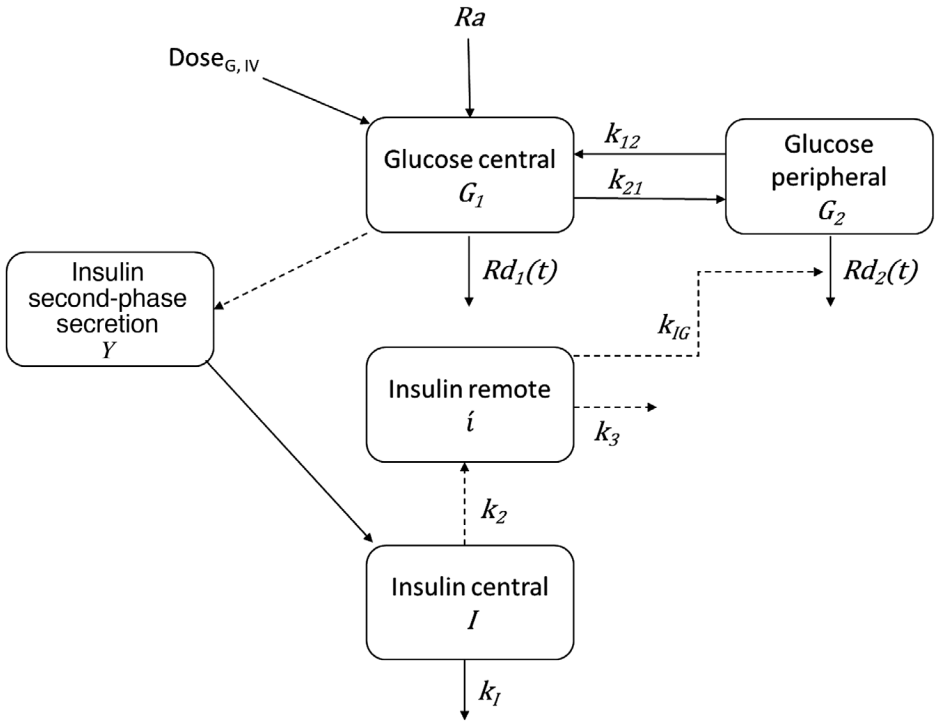

Figure 2. Schematic presentation of the integrated minimal model during IVGTT described in Appendix S2 by *Eq.* (*1b* − *10b*). G_1 and G_2, central and peripheral compartments of glucose; *I*, central compartment of insulin; *i*, insulin concentrations in the remote compartment; *Y*, second-phase insulin secretion; *Ra*, hepatic glucose production; Rd_1 and Rd_2, glucose elimination from central and peripheral compartments; k_{21} and k_{12}, glucose distribution parameters; k_2, k_3 and k_{IG}, parameters of insulin action; k_I, insulin elimination rate constant.

the same parameter certainty as in the optimized design. The reference designs in the current work were a standard rich and a standard sparse design (see the Study Design Optimization section).

Integrated Minimal Model

The development of the integrated minimal model has been described and published elsewhere,[8] as has the study from which the data to develop the model arose.[13] See below for a brief description. For more detail, see the original publications by Ibrahim et al[8] and Silber et al.[13] The details of the model, including equations, are available in Appendix S2.

The data came from an insulin-modified IVGTT. Forty-two patients with T2DM were recruited in a study. Most patients were obese, with a mean (standard deviation) weight of 89.4 kg (11.6). Patients on prior hypoglycemic medication underwent a 3-week washout before the start of the study. At the start, the patients displayed both hyperglycemia and hyperinsulinemia, with mean fasting glucose and insulin (standard deviation) of 183 mg/dL (44.3) and 13.5 mU/L (6.17), respectively. An intravenous bolus dose of glucose enriched with labeled glucose was administered, and blood samples for the determination of dynamic glucose and insulin were collected every minute from 2 to 6 minutes, every second minute from 6 to 12 minutes and 20 to 30 minutes, every third minute from 12 to 18 minutes, every fifth minute from 30 to 60 minutes, every 10th minute from 60 to 80 minutes, every 20th minute from 80 to 180 minutes, and every 30th minute from 180 to 240 minutes after glucose administration. This constitutes 32 samples, including the fasting sample; and this design is referred to as the standard design. The increased frequency of sampling 20 to 30 minutes after glucose administration is related to recombinant human insulin being administered 20 minutes into the study.

The integrated minimal model consists of 3 submodels: an insulin, a total glucose, and a labeled glucose submodel. The total and labeled glucose submodels share all disposition parameters, with the only difference being no endogenous glucose production for labeled glucose. The glucose and insulin are integrated through feedback mechanisms: Insulin stimulates glucose elimination from plasma, and glucose stimulates insulin secretion to plasma, both acting to keep the glucose homeostasis. Figure 2 is a schematic picture of the model.

Metabolic Indices

Glucose effectiveness S_G (mL/min) quantifies the ability of glucose to enhance its own rate of elimination at basal insulin concentration, and derived to be:

Table 1. Table of Designs

	SRD	SSD	Full Design Space	Optimized Rich Design		Optimized Sparse Design		Practical Design Space	Optimized Practical Rich Design		Realistic Design[c]	Optimized Practical Sparse Design	
				w rep	w/o rep	w rep	w/o rep		w rep	w/o rep		w rep	w/o rep[c]
Glucose dose, mg/kg	330	330	50-330	201	…	277	…	90[b]	…	…	…	…	…
Time of glucose dose, min	0	0	0-10	3.0	…	0.94	…	0[b]	…	…	…	…	…
Insulin dose [mU/kg]	30	30	0-180	103	…	158	…	24[b]	…	…	…	…	…
Time of insulin infusion [min]	20	20	0-240	0	…	0	…	20[b]	…	…	…	…	…
Insulin infusion duration [min]	5	5	1-240	75	…	71	…	5[b]	…	…	…	…	…
Number of samples	32	10		32	15	10	8		32	17	15	10	9
Efficiency relative to SRD	1	0.14		3.4	1.9	1.4	1.0		1.8	1.1	1.05	0.74	0.66
Efficiency relative to SSD	6.9	1	…	23	13	9.4	7.1	…	2.8	7.3	7.2	5.2	4.6

Standard rich design (SRD) and standard sparse design (SSD) are reference designs. Two design spaces were defined: a full flexible and a reduced, practical with restricted space for size and time of doses. Optimized rich design and optimized sparse design are optimizations from the full flexible design space while optimized practical rich design and optimized practical sparse design are based on the reduced, practical design space. the efficiency of a realistic design where also the duration between samples is taken into account as well as the efficiency when removing replicates[a] (w/o rep) are also listed.

[a]Replicate refers to repeated samples at the same time point.

[b]Parameters fixed during optimization.

[c]Recommended designs.

$$S_G = VG_1 \cdot \frac{k_{21}.k_{02}}{k_{02}+k_{12}}(0.241\gamma + 0.759) \quad (2)$$

Where VG_1(dL) is the volume of distribution for glucose, k_{02} (min) is the elimination rate constant of peripheral glucose, γ (unitless) is the ratio of central and peripheral glucose elimination rates at steady state and k_{12} (min) and k_{21} (min) are rate constants for disposition between central and peripheral glucose. Insulin sensitivity S_I (mL^2/mU/min) quantifies the influence of plasma insulin (at steady state) to change glucose's own effect on glucose concentration,[5] and is derived by:

$$S_I = VG_1 \cdot sk \cdot \frac{k_{21}.k_{12}}{(k_{02}+k_{12})^2} \quad (3)$$

in which sk (L/mU/min) is insulin sensitivity of peripheral glucose.

Study Design Optimization

The standard rich design, referred to in this work is identical to the design described above in the Integrated Minimal Model section, an insulin-modified IVGTT, starting with the administration of a bolus dose of glucose (0.33 g/kg), of which 10% is labeled glucose. A 5-minute insulin infusion (20 to 30 mU/kg) is initiated 20 minutes after glucose administration. A total of 32 samples for analysis of glucose, labeled glucose, and insulin concentrations are taken at 0, 2, 3, 4, 5, 6, 8, 10, 12, 15, 18, 20, 22, 24, 26, 28, 30, 35, 40, 45, 50, 55, 60, 70, 80, 100, 120, 140, 160, 180, 210, and 240 minutes after dosing. The standard sparse design differed only in the number of samples, which were 0, 2, 10, 15, 30, 45, 70, 100, 150, and 240 minutes after dosing. A study size of 42 patients was used for calculations of OFV. These patients were assumed to weigh 89.4 kg.[14]

For each optimized design, clinical trial simulations with 1000 patients were performed using the rich sampling times to evaluate the risk of hypoglycemia. The acceptable limit of hypoglycemia was <5% of the simulated patients having a glucose <58 mg/dL at any of the measurement times according to the standard rich design. This means that no more than 50 patients out of 1000 were allowed to have any measurement of glucose <58 mg/dL, not even for as short as 1 minute.

As the metabolic indices S_G and S_I depend on VG_1, k_{21}, k_{12}, k_{02}, γ, and sk, these parameters were set as the parameters of importance in the D_S-optimization. In the first optimization, the following aspects were evaluated simultaneously: glucose dose, labeled glucose dose, time for glucose dose, insulin dose, start time of insulin infusion, duration of insulin infusion, and sampling times. Thereafter, the labeled glucose dose was fixed to be 10% of the total glucose dose. All optimizations are summarized in Table 1.

Results

The integrated minimal model was successfully implemented in PopED, as evaluated by plotting glucose and insulin over time from the standard rich design (Figure 3). As seen in Figure 3, the model simulates patients with T2DM having fasting hyperinsulinemia, with a small increase in endogenous secretion (time 0 to 20 minutes) compared to concentrations of insulin after exogenous infusion (time >20 minutes). The difference

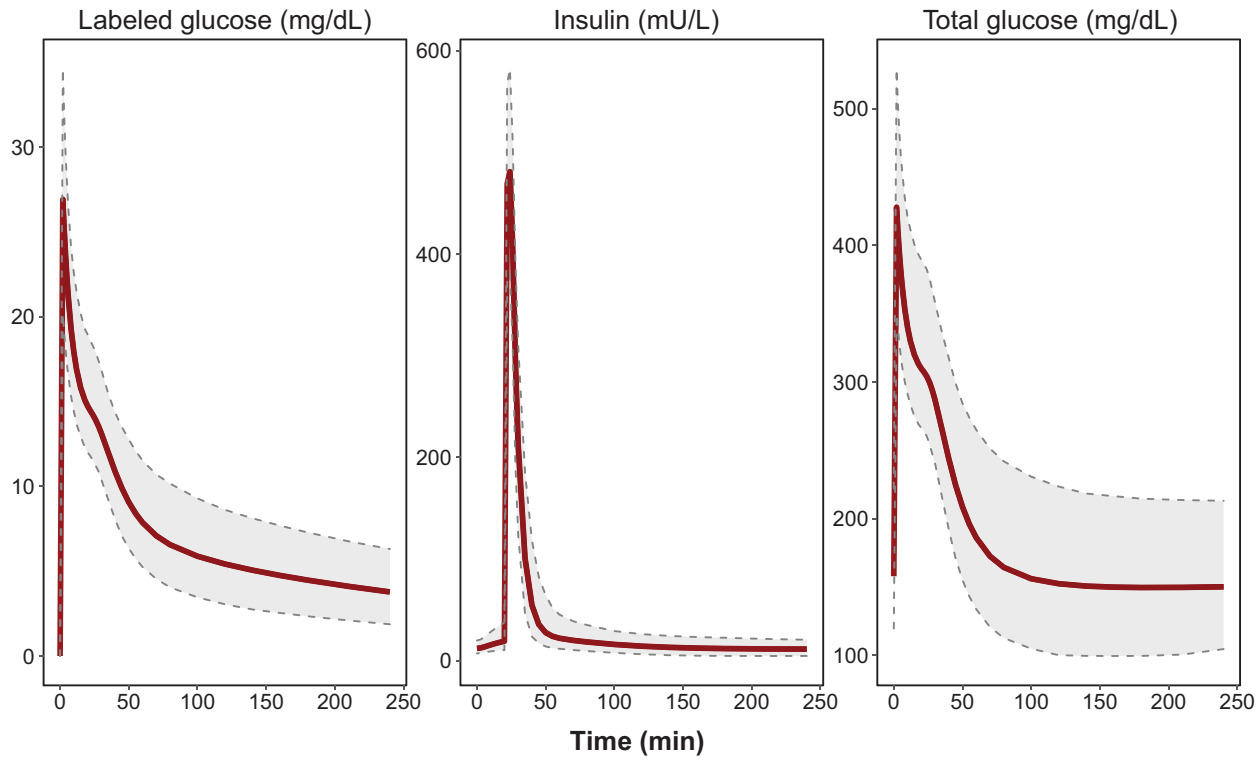

Figure 3. The model prediction plots for the integrated minimal model by PopED, showing that the model has been successfully implemented. The red line for population prediction and gray ribbon represent 90% prediction interval of the individual predictions. For this plot, 1000 individuals were simulated. The first plot shows the labeled glucose concentration (mg/dL), the second shows the insulin concentration (mU/L), and the third shows the total glucose concentration (mg/dL) over time.

in insulin concentrations before and after exogenous insulin is seen in the biphasic elimination phase of both total and labeled glucose. The insulin resistance is manifested with fasting hyperglycemia and hyperinsulinemia (time = 0 minute). The gray shaded area shows the between-subject variability.

In the first optimization, where the labeled glucose was allowed to vary, the optimized design included only a large dose of labeled glucose, as the valuable information obtained from administering labeled glucose allowed full description of glucose kinetics with unique separation of endogenous glucose production from glucose elimination; thus, cold glucose became unimportant. Hence, in the following optimizations we fixed the ratio between labeled and total glucose to the most commonly used ratio, 1:10.[13,15,16] With this condition set, the results of the optimizations are presented in Table 1.

On optimizing all design variables simultaneously without restrictions (left side of Table 1), all optimized designs included baseline measurement, followed by start of insulin infusion before glucose administration by ~3 and ~1 minute for the rich and sparse designs, respectively. Taking multiple samples at the same time, that is, replicates, gives information about between-sample variability and increases the efficiency. Removing replicates reduced the efficiency from 3.4 and 9.4 to 1.9 and 7.1 for the optimized rich and sparse designs, respectively, but the number of samples were also fewer (15 and 8, instead of 32 and 10 for rich and sparse, respectively).

In the optimized rich design, the glucose dose was 40% smaller, and insulin was 3.4 times higher than the standard glucose and insulin doses. The insulin infusion lasted 15 times longer; thus, the infusion rate was slightly smaller (1.50 mU/kg/min versus 1.37 mU/kg/min for standard and optimized, respectively). Such design pushed the system close to the most informative state for the parameters of interest but introduces hypoglycemia. Sampling times were focused in specific ranges (Table 2): around 0, 14 to 20, 42 to 44, and 230 to 240 minutes, with much fewer samples during the periods of rapid changes in glucose and insulin and focusing more on the periods where the feedback mechanisms are dominating, that is, the elimination phase, and hypoglycemia (time >108 minutes after study start). The efficiency was 3.4, meaning ~3 times more patients are needed with the SRD compared to the optimized rich design to achieve the same precision in S_G and S_I.

In the optimized sparse design, the higher doses of glucose and insulin were suggested compared to

Table 2. Table of Sampling Times[a]

Design	Sampling Times (min)
Standard rich — reference	0, 2, 3, 4, 5, 6, 8, 10, 12, 15, 18, 20, 22, 24, 26, 28, 30, 35, 40, 45, 50, 55, 60, 70, 80, 100, 120, 140, 160, 180, 210, 240
Optimized rich	0 (9), 6, 8, 15 (2), 20, 43, 44 (5), 78 (2), 108 (2), 147 (2) 220, 230 (2), 233, 235, 240
Optimized practical rich	0, 2, 3, 4, 12, 15 (3), 20, 22, 24, 24.5, 26, 28, 29, 44 (3), 100, 103 (5), 240 (7)
Realistic[b]	0, 2, 4, 12, 15, 20, 22, 24, 26, 28, 30, 44, 100, 103, 240
Standard sparse — reference	0, 2, 10, 15, 30, 45, 70, 100, 150, 240
Optimized sparse	0 (2), 1, 15, 74 (2), 93, 137, 230, 240
Optimized practical sparse[b]	0, 2, 15 (2), 30, 45, 100, 103, 211, 230

Number of replicates in a sampling time is given in parentheses.
[a]Replicate: sample analyzed repeatedly from the same time.
[b]Recommended designs, without replicate samples.

the optimized rich design. Glucose dose was 83% of standard glucose dose, insulin dose 5.2 times the standard insulin dose, and infusion duration was 14.2 times longer than the standard infusion duration. Thus, in this design the insulin infusion rate was higher (2.24 mU/kg/min). Samples were picked as follows: 2 samples at start of insulin infusion, 1 sample at glucose administration, 1 sample at early elimination phase, and 6 samples in hypoglycemia conditions (time >70). The efficiency was 9.4, that is, ~9 times more patients are needed with the standard sparse design compared to the optimized sparse design to achieve the same precision in interesting parameters. Furthermore, the optimized sparse design was more efficient than the SRD (efficiency 1.4), despite 22 fewer samples.

However, 55% and 78% of simulated patients of the optimized rich and sparse designs, respectively, showed hypoglycemia, which is unacceptable in a design. To address this design problem, a range of simulations with varying glucose and insulin doses were performed, determining a design with low risk of hypoglycemia and high efficiency. This resulted in a practical design with 73% and 20% lower glucose (90 mg/kg) and insulin dose (24 mU/kg), respectively, with glucose given at 0 minute and insulin given as a 5 minutes infusion at 20 minutes. This design caused hypoglycemia in less than 2% of the simulated patients (Figure 4). The average glucose concentration-time profile following the 4 different designs: standard design, optimized rich design, optimized sparse design and the practical design, are shown in Figure 5. Two designs were deduced from the practical design: rich and sparse design where only the sampling times were optimized (right side of Table 1). Finally, the optimized practical rich design without replicates was 1.10 times as efficient as SRD. The interpretation of this is that by lowering the glucose and insulin dose, 10% fewer patients can be included in a study, and 15 fewer samples can be taken with maintained precision of estimates related to glucose effectiveness and insulin sensitivity.

The theoretically expected precision of the interesting parameters under each design using 42 patients is shown in the Appendix S3. All optimized designs showed good precision even with sparse sampling; thus, using optimized designs with low efficiency would still provide well-estimated parameters, with 42 patients.

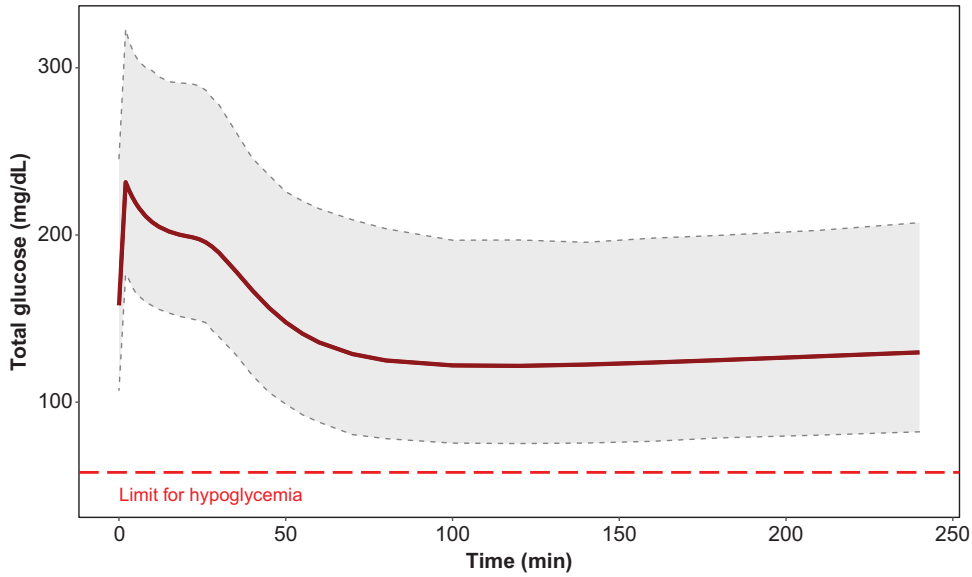

Figure 4. 1000 individual predictions of glucose concentration-time profiles under a practical design with lowered doses, glucose dose 90 mg/kg given at time 0, and insulin infusion of 24 mU/kg started at 20 minutes, for 5 minutes.

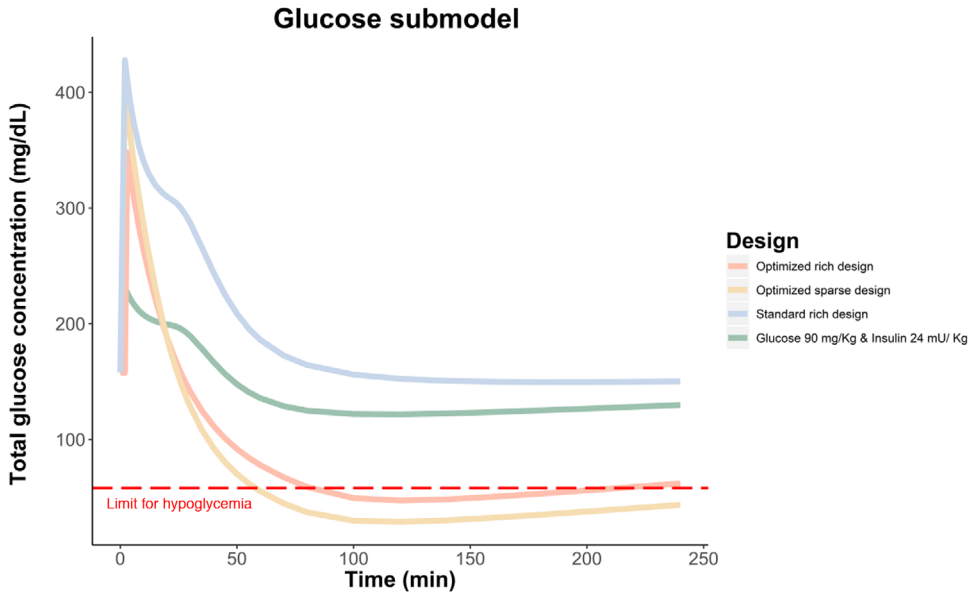

Figure 5. Plots of the average glucose concentration time profile under different designs using the rich sampling times. A practical design with glucose dose 90 mg/kg given at time 0, and insulin infusion of 24 mU/kg started at 20 minutes, for 5 minutes, showed a hypoglycemia less likely profiles than both the optimized rich design and optimized sparse design.

The improvement was substantial for k_{02} and γ that had extremely poor expected precision under standard designs.

Discussion

Intravenous glucose tolerance test has been extensively used in diabetes research as the conventional provocation for quantifying glucose-insulin regulation system functionality. Although IVGTT design focuses mainly on exploring the clearance of glucose from the blood and does not allow direct assessment of insulin sensitivity, coupling IVGTT with the minimal models makes it possible to predict insulin sensitivity and glucose effectiveness. Since the first use of IVGTT with the minimal models, the IVGTT design has gone through a couple of refinements, aiming to reduce its intense sampling schedule while retaining its information content. To our knowledge, this work is the first to optimize the design of IVGTT for model-based assessment of S_G and S_I with respect to all design variables simultaneously, which has previously been suggested, but not performed.[14,17] We concluded 2 patient-convenient, informative designs with lower doses and fewer samples for precise estimation of glucose effectiveness and insulin sensitivity. However, these designs are still yet to be tested in a clinical setting.

Just by looking at the parameters of interest, we can deduce that samples after glucose administration would be informative of VG_1 and distribution parameters, samples before insulin administration would be informative of parameters related to glucose effectiveness, samples after start of insulin infusion would be informative of insulin sensitivity, and finally samples at baseline, end of study, and where hypoglycemia occurs ($\sim$100 minutes) would be informative of γ and glucose disposition and elimination parameters. Thus, these are the time intervals expected to be intensely sampled when optimizing for S_G and S_I, and this was also what our optimization determined to be the best design. When optimizing all variables simultaneously allowing rich sampling, the optimized design showed substantial increase in efficiency, reaching $\sim$3.4 times the efficiency of the SRD. This means that 3.4 times fewer number of patients are needed with an optimized design compared to the standard design. After removing replicates, the efficiency dropped to $\sim$1.9, but with a reduction of samples; from 32 to 15, which still is a remarkable improvement. Similar results were seen in all situations where replicates were removed, as shown in Table 1. Thus, we recommend considering replicate samples to improve precision of parameters without increased discomfort for the patients.

In this work, simulations were performed to identify designs with lower risk of hypoglycemia, and a practical design with lower glucose and insulin doses was deduced for further optimization. This is not an optimal design, by definition, but a practically feasible design, close to optimal. An alternative approach would be defining a cost function where a lower boundary of allowed glucose concentrations is defined, basing the optimization on this function. On optimizing the practical design with a rich sampling schedule, removing replicates, only 17 samples remained: 0, 2, 3, 4,

12, 15, 20, 22, 24, 24.5, 26, 28, 29, 44, 100, 103, and 240 minutes. Since it would be practically challenging to sample every minute, or half-minute, we tweaked this optimal sampling schedule into a more realistic sampling schedule: 0, 2, 4, 12, 15, 20, 22, 24, 26, 28, 30, 44, 100, 103, and 240, which was 1.05 times more efficient than the standard rich design with 32 samples. Thus, by reducing the glucose and insulin dose and taking the samples at more realistic times, it is possible to get the same precision of parameters determining S_G and S_I with 15 instead of 32 samples.

As mentioned in the introduction, by adopting D-optimality criterion for the 1-compartment labeled-glucose minimal model and fixing other design variables, Cobelli and Ruggeri[6] concluded a sampling schedule of 14 samples: 2, 3, 4, 5, 8, 10, 18, 20, 28, 32, 40, 60, 70 and 240 minutes. Similar to our sampling schedule, only 4 samples were after ~30 minutes. The absence of distribution parameters in the 1-compartment model was clearly the reason for the earlier shifting of the sampling times in their results. The model we used in the work has the advantage of being an integrated portrait of the glucose insulin system, thus not conditioned on insulin observations. This gives us the possibility to, apart from optimizing on insulin and glucose simultaneously, optimize designs for populations with endogenous insulin. Our integrated model is using the 2-compartment labeled glucose minimal model which superiority over its 1-compartment version has previously been elaborately explained.[18,19] In addition, we used a D_S-optimality criterion to focus our optimization on the interesting parameters S_G and S_I and deduced lower doses for glucose and insulin. Another interesting optimization of IVGTT was performed by Silber et al[14] using a different mathematical model, the integrated glucose-insulin model. However, they could not perform a simultaneous optimization of all design variables, instead they used a sequential approach. That was reflected in their results as higher doses of glucose and/or insulin with varying sampling schedules (each of 10 samples) were found to be the most efficient. The lower doses of glucose and insulin in our results were deduced thanks to the initial simultaneous optimization of all design variables. Also, the optimizations by Silber et al did not aim at finding designs for the precise estimation of S_G and S_I, as these parameters are not part of the integrated glucose-insulin model.

It is important to stress that the predicted precision of parameters (Appendix S3) were similar for all optimized designs, despite large differences in efficiency. Thus, for the assessment of S_G and S_I, the use of the optimized practical sparse design without replicates would result in satisfactory precision even though being 44% less efficient than the SRD. This is related to the study population size. The calculations apply for a study with 42 patients, and according to these predictions, the SRD would need only ~20 patients for equally precise estimates. Although the study population size in this work was large, the results of efficiency are valid for other study population sizes; only the actual precision of the parameters (Appendix S3) will depend on the study population size. Similar results were reported previously by Silber et al[13] as one of the main findings were the good parameters precision of optimized sparse designs. This previous analysis was performed assuming population analysis, as in our work, as opposed to other optimizations, assuming standard two-stage analysis. The population analysis approach showed greater precision than standard two-stage approach when both were applied to a reduced sampling IVGTT minimal modeling.[7]

In conclusion, 2 optimized IVGTT designs for model-based assessment of S_G and S_I by the integrated minimal model were presented: the realistic design and the optimized practical sparse design without replicates. These designs are 1.05 and 4.6 times more efficient than standard rich and sparse designs, respectively, with reduced resources and reduced discomfort for the patients, constrained to prevent hypoglycemia and providing precisely estimated parameters.

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Conflicts of Interest

The authors declare no conflicts of interest.

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Data Sharing

In this work, the study design of the IVGTT has been optimized for determination of the insulin sensitivity and glucose effectiveness. In doing so, the integrated minimal model was used, but there are no data, and thus data sharing is not applicable to this work.

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