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ORIGINAL ARTICLE

A Simple Robust Method for Estimating the Glucose Rate of Appearance from Mixed Meals

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Abstract

Background:

Estimating the rate of glucose appearance (R_a) after ingestion of a mixed meal may be highly valuable in diabetes management. The gold standard technique for estimating R_a is the use of a multitracer oral glucose protocol. However, this technique is complex and is usually not convenient for large studies. Alternatively, a simpler approach based on the glucose-insulin minimal model is available. The main drawback of this last approach is that it also requires a gastrointestinal model, something that may lead to identifiability problems.

Methods:

In this article, we present an alternative, easy-to-use method based on the glucose-insulin minimal model for estimation of R_a. This new technique avoids complex experimental protocols by only requiring data from a standard meal tolerance test. Unlike other model-based approaches, this new approach does not require a gastrointestinal model, which leads to a much simpler solution. Furthermore, this novel technique requires the identification of only one parameter of the minimal model because the rest of the model parameters are considered to have small variability. In order to account for such variability as well as to account for errors associated to measurements, interval analysis has been employed.

Results:

The current technique has been validated using data from a United States Food and Drug Administration-accepted type 1 diabetes simulator [root mean square error (RMSE) = 0.77] and successfully tested with two clinical data sets from the literature (RMSE = 0.69).

Conclusions:

The presented technique for the estimation of R_a showed excellent results when tested with simulated and actual clinical data. The simplicity of this new technique makes it suitable for large clinical research studies for the evaluation of the role of R_a in patients with impairments in glucose metabolism. In addition, this technique is being used to build a model library of mixed meals that could be incorporated into diabetic subject simulators in order to account for more realistic and varied meals.

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Abbreviations: (AUC) area under the curve, (CV) coefficient of variation, (FDA) Food and Drug Administration, (MIA) model interval analysis, (MTT) meal tolerance test, (OGTT) oral glucose tolerance test, (R_a) glucose rate of appearance, (RMSE) root mean square error, (SD) standard deviation, (S_I) insulin sensitivity, (T1DM) type 1 diabetes mellitus, (UVa) University of Virginia

Keywords: artificial pancreas, diabetes management, glucose rate of appearance, insulin sensitivity, robust estimation

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Introduction

Estimating the rate of glucose appearance (R_a) into the systemic circulation after ingestion of a mixed meal may be highly valuable in diabetes management as well as in other pathophysiological states (e.g., abnormalities of glucose absorption). For instance, in the context of an artificial pancreas,[1] it is of great importance to estimate the contribution of the ingestion of a mixed meal into the overall glucose kinetics because an accurate prediction of plasma glucose is crucial to the performance of most glucose controllers.[2]

The gold standard technique for estimating prior R_a is the use of a multitracer oral glucose protocol.[3] However, this technique is complex and usually not convenient for large studies (e.g., screening studies). Alternatively, a simpler approach[4] based on the glucose-insulin minimal model[5] is available. This approach only requires plasma glucose and plasma insulin data acquired from an oral glucose tolerance test (OGTT) or meal tolerance test (MTT). The main drawback of this approach is that it requires a gastrointestinal absorption model coupled to the minimal model of glucose disappearance, which leads to a large number of model parameters that need to be identified. This problem is usually overcome by using sophisticated parameter identification techniques (e.g., Bayesian estimation), which usually require a number of assumptions over the parameters (e.g., probability distribution).

In this article, a novel minimal model approach for estimating R_a is proposed. The main advantage of this new approach is that it does not require a gastrointestinal model. This difference leads to a much simpler solution because complex parameter identification techniques are not required. This technique provides an estimate of R_a, which can then be used to fit the model parameters for any existing gastrointestinal models.[6–9]

The proposed approach for estimating R_a requires only the identification of insulin sensitivity (S_I) from the minimal model because it is based on the hypothesis that the rest of the model parameters can be considered to vary in relatively small ranges. This hypothesis is based on the experimental evidence that the intersubject variability of these parameters is not very big.[3] In order to validate this hypothesis, interval analysis[10] was employed to obtain a robust estimation of R_a accounting for the intersubject variability on the model parameters. Furthermore, interval analysis also allows accounting for the errors associated with the measurements.

For estimating S_I, the existing formula proposed by Caumo and colleagues[11] could be used. However, the procedure to obtain this formula requires an assumption on the shape of the R_a, which may not be suitable for our approach because estimating R_a is the objective. For this reason, we present a new formula for estimating S_I that does not require any assumption on the R_a profile.

To validate the technique, a United States Food and Drug Administration (FDA)-accepted University of Virginia (UVa) simulator of subjects with type 1 diabetes mellitus (T1DM)[12] has been employed to generate the required data. Furthermore, the new methodology has been tested using clinical data obtained from the literature.[4,13]

Methods

Minimal Model of Glucose Disappearance

The minimal model of glucose disappearance from a frequently sampled intravenous glucose tolerance test is widely used to assess S_I and glucose effectiveness (S_G) in physiological, pathophysiological, and epidemiological studies.[14] The minimal model is represented by the equations

$$\dot{G}(t) = -[S_G + X(t)]G(t) + S_G G_b + \frac{R_a(t)}{V} \quad (1)$$

$$\dot{X}(t) = -p_2 X(t) + p_2 S_I [I(t) - I_b] \quad (2)$$

where G(mg/dl) is plasma glucose concentration with $G(0) = G_b$; I (μU/ml) is plasma insulin concentration with $I(0) = I_b$, where suffix b denotes basal values; X is insulin action on glucose production and disposal with $X(0) = 0$; V (dl/kg) is the distribution volume; and S_G (min^{-1}), S_I (min^{-1} per μU/ml), and p_2 (min^{-1}) are model parameters. Specifically, S_G (min^{-1}) is the fractional (i.e., per unit distribution volume) glucose effectiveness, which measures glucose ability *per se* to promote glucose disposal and inhibit glucose production; S_I is insulin sensitivity; p_2 is the rate constant describing the dynamics of insulin action; and R_a (mg/min) is the rate of glucose appearance.

Glucose Rate of Appearance Estimation

From **Equation (1)**, R_a can be isolated as follows:

$$R_a(t) = [\dot{G}(t) + [S_G + X(t)]G(t) - S_G G_b]V \quad (3)$$

In order to evaluate **Equation (3)**, a number of assumptions need to be made. As discussed in detail by Dalla Man and collegues,[3] one can assume mean population values for parameters V, p_2, and S_G because their interpatient variability is not very large. On the other hand, the variability of S_I is much larger, and this parameter needs to be individualized for each subject.

The following assumption can be made if the duration of the OGTT/MTT experiment is long enough to consider that the ingested carbohydrate has been fully absorbed:

$$\int_0^T R_a(t)dt = fD \quad (4)$$

where f (unitless) is carbohydrate bioavailability (i.e., fraction of carbohydrate absorbed), D (mg) is the amount of ingested carbohydrates, and T (min) is the duration of the experiment.

By replacing **Equation (3)** into **Equation (4)**,

$$\int_0^T \left(\dot{G}(t) + [S_G + X(t)]G(t) - S_G G_b \right) V dt = fD \quad (5)$$

Defining $I'(t)$ as $[I(t) - I_b]$, **Equation (2)** becomes

$$\dot{X}(t) = -p_2 X(t) + p_2 S_I I'(t) \quad (6)$$

which, by applying the Laplace transform, can be expressed as

$$\frac{X(s)}{I'(s)} = S_I \frac{p_2}{s + p_2} \quad (7)$$

The impulse response of **Equation (7)** is

$$\zeta^{-1}\left\{\frac{X(s)}{I'(s)}\right\} = S_I p_2 e^{-p_2 t} \quad (8)$$

and solution of **Equation (6)**, for $X(0) = 0$, is expressed by the convolution integral

$$X(t) = S_I \int_0^t p_2 e^{-p_2 t} I'(t - \tau)d\tau \quad (9)$$

By replacing **Equation (9)** into **Equation (5)**,

$$\int_0^T \dot{G}(t)dt + \int_0^T S_G G(t)dt + S_1 \int_0^T \left[\int_0^t p_2 e^{-p_2 \tau} I'(t - \tau)d\tau \right] G(t)dt - \int_0^T S_G G_b dt = \frac{fD}{V} \quad (10)$$

By isolating S_I from **Equation (10)**,

$$S_I = \frac{\frac{fD}{V} - \int_0^T \dot{G}(t)dt - \int_0^T S_G G(t)dt + \int_0^T S_G G_b dt}{\int_0^T \left[\int_0^t p_2 e^{-p_2 \tau} I'(t - \tau)d\tau \right] G(t)dt} \quad (11)$$

which is equivalent to

$$S_I = \frac{\frac{fD}{V} - [G(T) - G(0)] - \int_0^T S_G G(t)dt + S_G G_b T}{\int_0^T \left[\int_0^t p_2 e^{-p_2 \tau} I'(t - \tau)d\tau \right] G(t)dt} \quad (12)$$

Now, S_I can be easily evaluated with **Equation (12)** and standard data obtained from an OGTT/MTT test, considering a basal initial condition. Finally, R_a can be calculated by substituting **Equation (9)** into **Equation (3)** as follows:

$$R_a(t) = V \left(\dot{G}(t) - S_G G_b + \left[S_G + S_I \int_0^t p_2 e^{-p_2 \tau} I'(t - \tau)d\tau \right] \right) \quad (13)$$

In order to evaluate **Equation (12)** and **Equation (13)**, the Euler approximation method, with a step size of 1 minute, was employed. Cubic splines were used to interpolate both G and I signals. The derivative of G was approximated by the slope of linear regression of 10 consecutive interpolated G values. In order to reduce the effect of the noise on the derivative of G, the derivative filter differentiator from the MATLAB® Signal Processing Toolbox was used (2010b, The MathWorks, Inc., Natick, MA). The full algorithm was implemented using MATLAB.

Robustness Analysis via Interval Analysis

As stated earlier, mean population values can be assumed for parameters V, p_2, and S_G because their interpatient variability is not very large.[4] Nevertheless, in order to evaluate the effect of this variability on estimation of R_a

as well as the measurements error, we propose the use of interval analysis.[13] Interval analysis is a mathematical tool that has been applied extensively in the field of robust control as a way to deal with uncertainty.[15]

Interval analysis allows representing uncertainties by means of intervals represented by a lower and upper limit; thus, in using intervals, no assumptions are made about the probability distribution of the uncertainties or about the independence or correlation of parameters.

Simulation of a model involving interval values produces a band (or envelope) that represents the evolution of each state variable over time and, unlike Monte Carlo techniques, numerically guarantees that all the behaviors are considered. In particular, we have used modal interval analysis (MIA) because it allows for more efficient computations than the classical interval approach[10] (for a complete introduction to MIA, see Gardenyes and colleagues[16]). Model interval analysis has already been successfully applied for the prediction of postprandial glucose excursions under uncertainty in T1DM[17] and for optimization of insulin dosage based on these predictions.[18]

In-Silico *Validation*

The proposed technique has been validated using simulated data from the FDA-accepted UVa T1DM simulator,[12] hereafter T1DM simulator. Note that the T1DM model implemented in the simulator[19] is different from the minimal model because the former incorporates endogenous glucose production, renal excretion, and insulin-independent and -dependent glucose utilization. This makes the T1DM simulator a suitable platform for validating the proposed approach for estimating R_a.

The T1DM simulator was used to generate the required data (i.e., plasma insulin, plasma glucose, and R_a) from a MTT. For this purpose, the 10 adult diabetic subjects of the commercial version of the T1DM simulator were used. The metabolic test functionality provided by the simulator was employed for this purpose. The protocol applied consisted of adjusting the basal insulin rate in order to get a basal glucose level (G_b) close to 100 mg/dl. The amount of carbohydrates ingested was fixed to 50 g, and the corresponding insulin bolus was adjusted in order to minimize the postprandial peak and to avoid a big inverse peak response (i.e., undershoot below 80 mg/dl). The total time for the experimental period was adjusted in order to return to the basal states after the ingestion of the meal (i.e., 6 h). Note that despite ingesting the same amount of carbohydrates, the glucose absorption rate for each individual of the simulator may be significantly different.

Once the basal conditions were achieved by applying the protocol described earlier, basal plasma glucose and plasma insulin levels (G_b and I_b) were obtained from the simulator.

Because plasma glucose and plasma insulin data provided by the simulator are error-free, ±2 and ±4% uniformly distributed errors were added to the plasma glucose and plasma insulin measurements, respectively, as reported in YSI Life Sciences[20] and Even and colleagues.[21]

S_I *Estimation*

The proposed technique for estimating S_I (**Equation 12**) was compared against the clinically validated method proposed by Caumo and colleagues.[11] For this purpose, the minimal model parameters values reported by Krudys and colleagues[22] for a T1DM subject (i.e., S_G = 0.014 min^{-1}, V = 1.7 dl/kg, and p_2 = 0.03 min^{-1}) were used. The carbohydrate bioavailability (f) was assumed to be 0.9 because this is a standard value for mixed meals.[4]

The coefficient of determination between the two techniques was R^2 = 0.99. Despite the two methods seeming to be equivalent, we still consider that our approach is methodologically more robust because it does not require any *a priori* assumption on R_a.

Interval R_a *Estimation*

Intervals associated to model parameters V, p_2, and S_G were defined based on the intersubject variability reported by Dalla Man and colleagues[4] [i.e., (V) coefficient of variation (CV) = 4%; (p_2) CV = 11%; and (S_G) CV = 12%], being the associated interval defined as

$$Interval = [mean - SD, mean + SD] \quad (17)$$

where mean is the reported mean value for the model parameter[22] and SD is the corresponding standard deviation. One standard deviation was selected to generate such intervals since this was considered enough to encompass most of the possible behaviors.

Intervals corresponding to plasma glucose and plasma insulin measurements were defined based on the errors [(G) ±2% and (I) ±4%] reported in YSI Life Sciences[20]

and Even and colleagues,[21] with the associated interval defined as

$$Interval = [mean - \%mean,\ mean + \%mean] \quad (18)$$

In order to account for the variability of S_I due to error in the measurements, a simulation study was carried out comparing estimated S_I with error and without error in the measurements. The resulting CV was 16%. The corresponding interval was calculated using **Equation (17)**.

Finally, a ±5% variability was considered for the carbohydrate bioavailability, f, and a ±10% error for the estimation of the glucose derivative, based on empirical observations.

Figure 1 shows the intervals associated with plasma glucose, plasma insulin measurements, and estimation of the glucose derivative.

Experimental Tests

The technique presented has also been tested with clinical data. For this purpose, the scientific literature was reviewed for published clinical trials, including R_a data obtained with a multitracer oral protocol, plasma glucose and plasma insulin concentration data, meal composition, and body weight. Despite an intensive bibliographic search, only two studies[4,13] were found that satisfied these criteria.

The first selected study[4] (study 1) involved 88 normal glucose tolerance subjects (46 males and 42 females; age = 58 ± 2 years; body weight = 77 ± 2 kg) who received

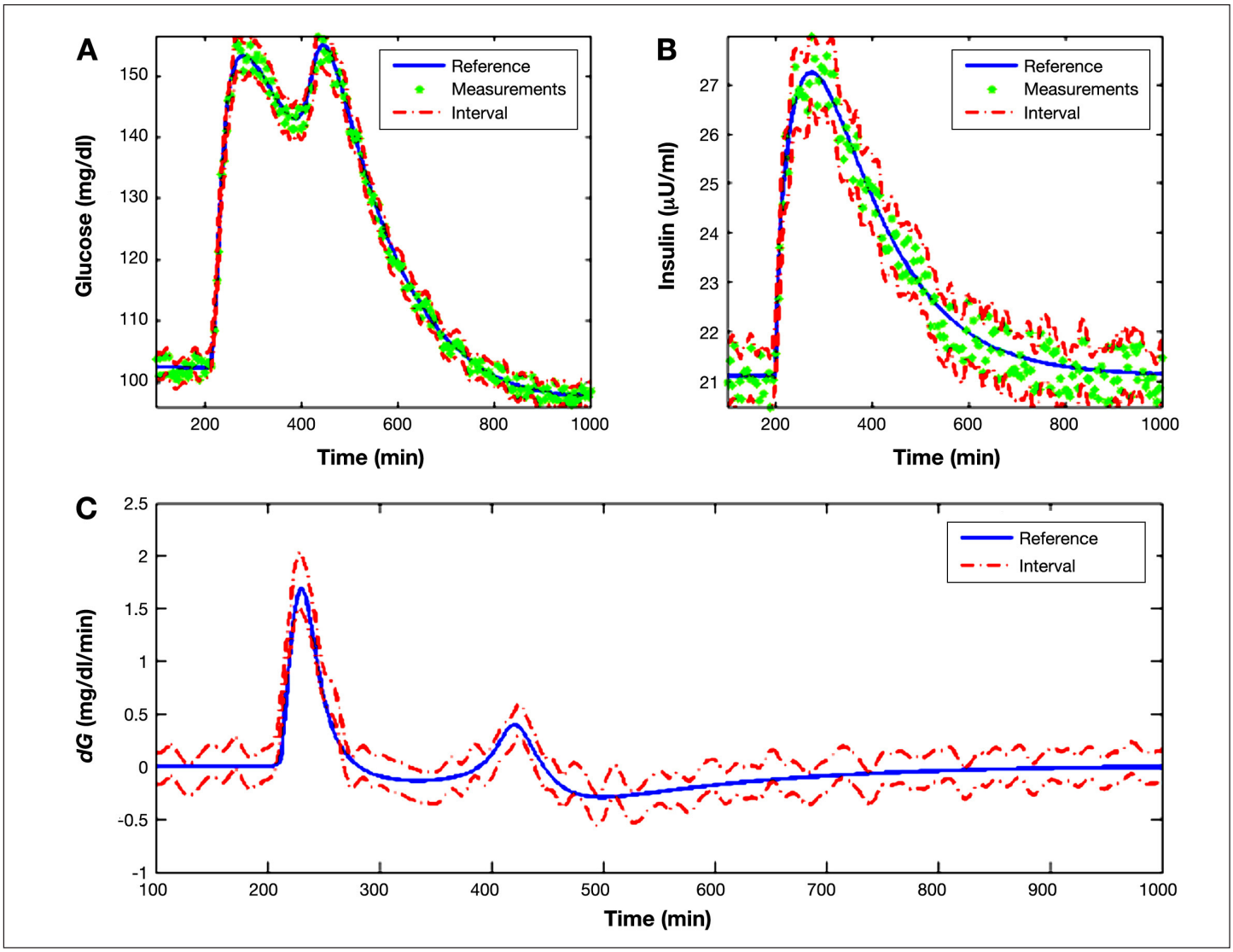

Figure 1. Intervals (dashed red lines) associated with plasma glucose **(A)**, plasma insulin **(B)** measurements, and estimation of the glucose derivative **(C)**.

a triple-tracer mixed meal (10 kcal/kg, 45% carbohydrate, 15% protein, and 40% fat) containing 1 ± 0.02 g/kg glucose (77 ± 1.54 g). The second study[12] (study 2) involved 21 nondiabetic subjects (13 males and 8 females; age = 41 ± 1 years; body mass index = 27 ± 1 kg/m^2) with varying degrees of glucose tolerance (10 normal glucose tolerance and 11 impaired glucose tolerance) who underwent an OGTT labeled with two glucose tracers.

S_G, p_2, and V minimal model parameters were fixed to the mean population values for a normal glucose-tolerant subject reported by Dalla Man and colleagues (i.e., S_G = 0.029 min^{-1}, V = 1.4 dl/kg, and p_2 = 0.0123 min^{-1}).[4] Note that for study 2, neither the body weight nor the carbohydrate amounts are provided in the article. Because the study consisted of a standard meal tolerance test, the amount of carbohydrate was considered to be 75 g. The corresponding intervals were defined in the same manner as with the *in-silico* validation tests (see ***Interval* R_a *Estimation***). The employed glucose and insulin data correspond to average population data.

Results

In-Silico *Results*

Table 1 shows the relative root mean square error (RMSE) between the center of the R_a interval estimations and the reference R_a corresponding to the 10 adult subjects of the simulator. In the same table, the area under the curve (AUC) of the estimated R_a is also reported as well as the percentage of time that the reference R_a remains inside of the interval estimate. Note that the reference value of absorbed amount of carbohydrates is 45 g and not 50 g because of the carbohydrate bioavailability (f = 0.9).

Figures 2 and **Figure 3** show the interval R_a estimations for adults number 1 and number 2 of the simulator, the center of the interval estimate, the reference R_a profiles, and corresponding plasma glucose and plasma insulin data. First of all, note that the reference behavior is, practically all the time, fully included inside the interval estimate. Furthermore, note that despite the relatively big size of the obtained interval estimate, the center of the interval fits well with the reference behavior.

Experimental Results

The relative RMSE between the center of the interval R_a estimation and the reference R_a for studies 1 and 2 were RMSE = 0.61 and RMSE = 0.77, respectively. The respective AUC for each study were AUC_1 = 71.5 g and AUC_2 = 68.8 g, while the reference amount of absorbed carbohydrates were 78.5 g and 66.9 g. In both studies, the percentage in time corresponding to the reference R_a inside the interval estimate was 95%. Note that the reference R_a deviates out of the interval estimate when it initially increases rapidly. This effect is probably due to the filtering of the derivative of G, which advances the signal, as can be observed in **Figure 1**.

Figure 4 and **Figure 5** show the interval R_a estimations for both studies together with the corresponding reference R_a estimated with tracers.

Discussion

The methodology presented has been proven to be a simple and effective way to estimate the rate of glucose appearance from mixed meals. The simplicity of this technique makes it suitable for large clinical research studies for the evaluation of the role of R_a in patients with impairments in glucose metabolism. Note that the proposed methodology is limited to in-clinic studies as it requires plasma glucose and plasma insulin data. To obtain satisfactory results, it is important to capture the complete glucose and insulin dynamics during the experiments. For this purpose, the sampling time and duration of the experiment have to be carefully selected. Finally, when dealing with glucose-intolerant subjects, it is important to guarantee that basal conditions are satisfied at the start and end of the experiment.

Table 1.
RMSE between the Center of the R_a Interval Estimation and the Reference R_a; AUC of the Center of the R_a Interval Estimate and Percentage in Time of the Reference R_a inside the Interval Estimate Corresponding to the 10 Adult Subjects of the Simulator

Subject	#1	#2	#3	#4	#5	#6	#7	#8	#9	#10	Mean
RMSE	0.78	0.8	0.77	0.78	0.79	0.74	0.8	0.75	0.72	0.79	0.77
AUC (R_a)	48.3	46.7	45.8	47	47.6	45	47.5	45.5	46.2	46.2	46.5
% Time	99	100	99	99	100	98	99	100	100	100	99

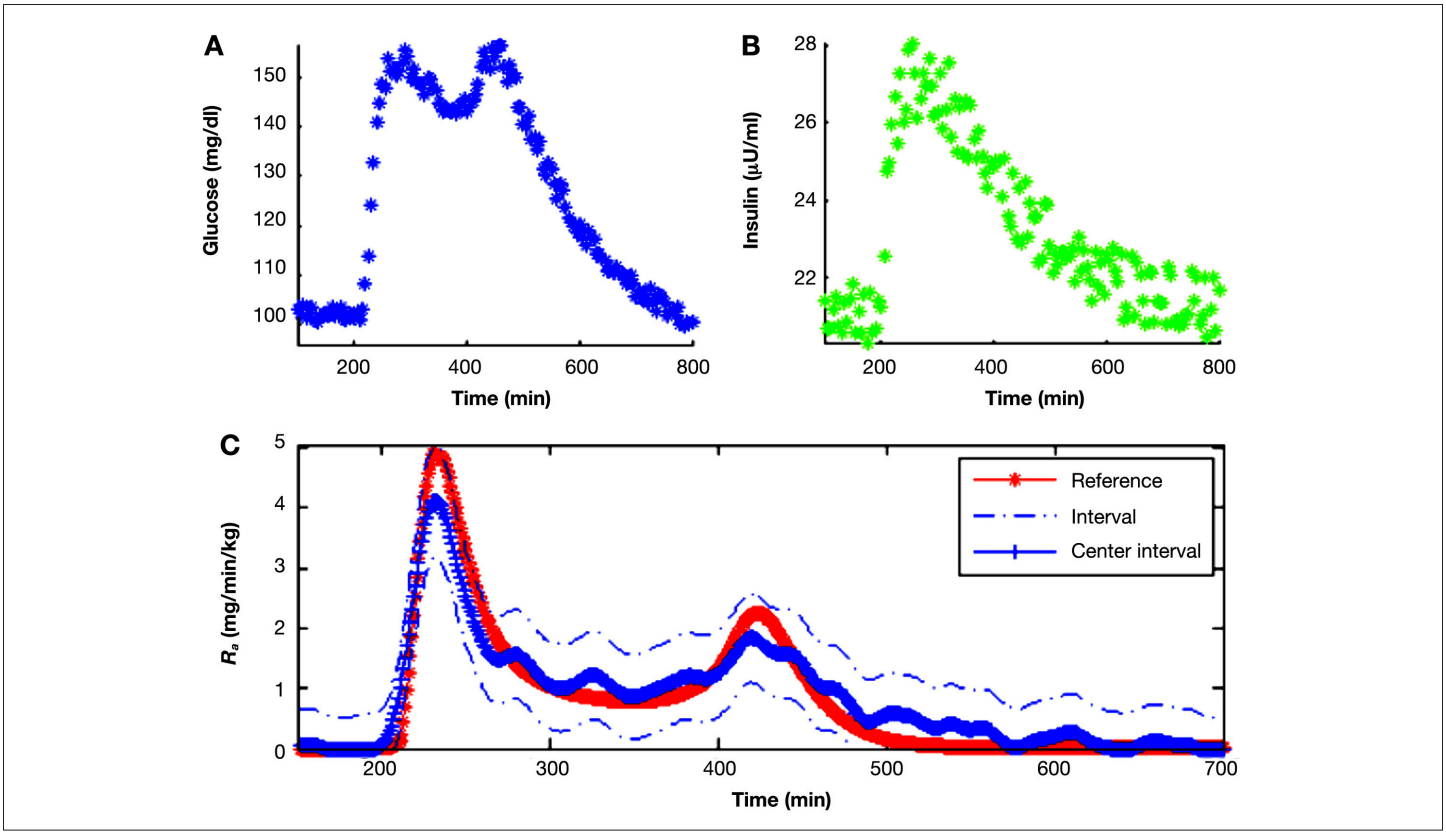

Figure 2. Interval R_a estimation for adult 1 **(C)**, plasma glucose **(A)**, and plasma insulin **(B)**.

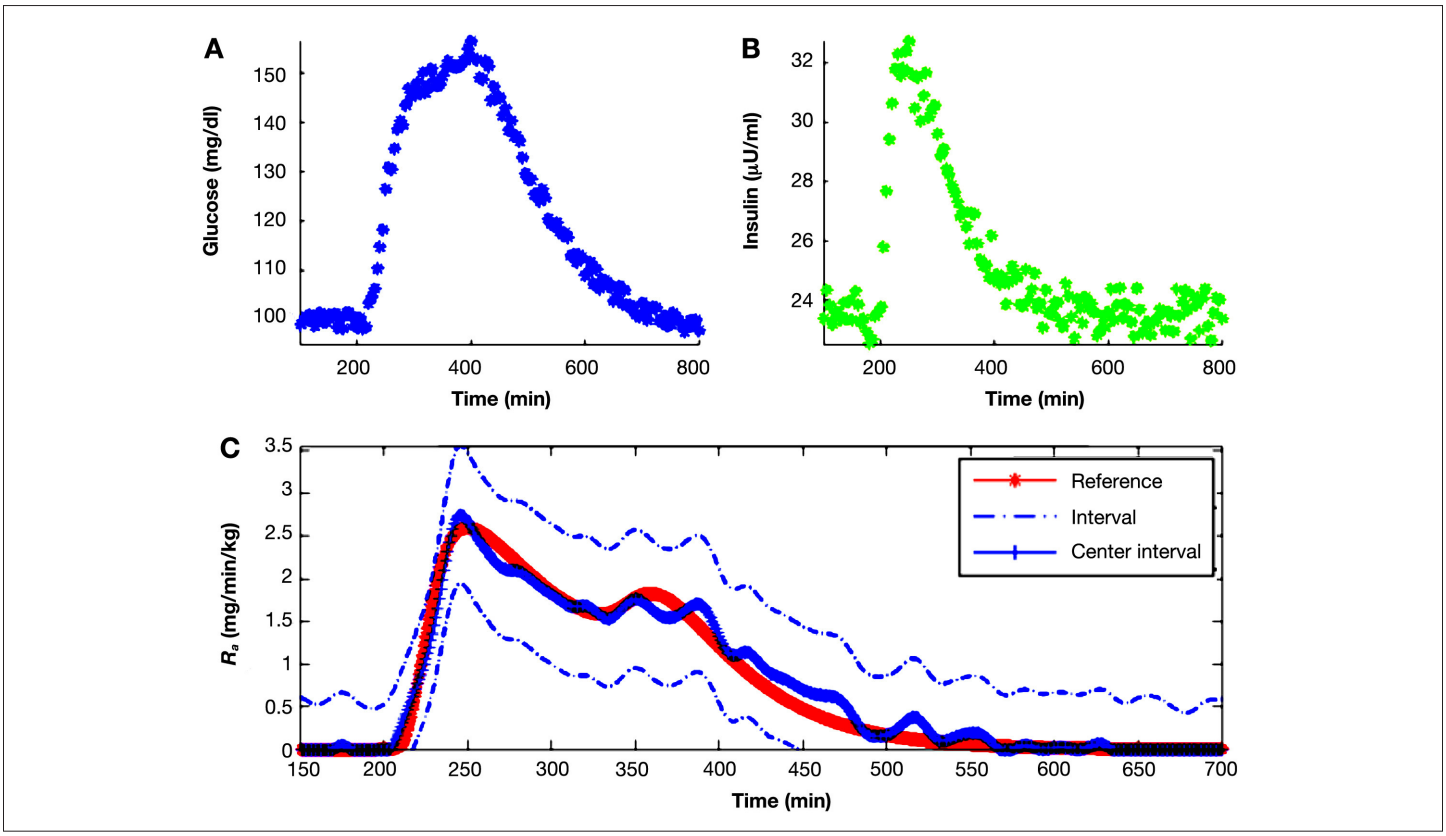

Figure 3. Interval R_a estimation for adult 2 **(C)**, plasma glucose **(A)**, and plasma insulin **(B)**.

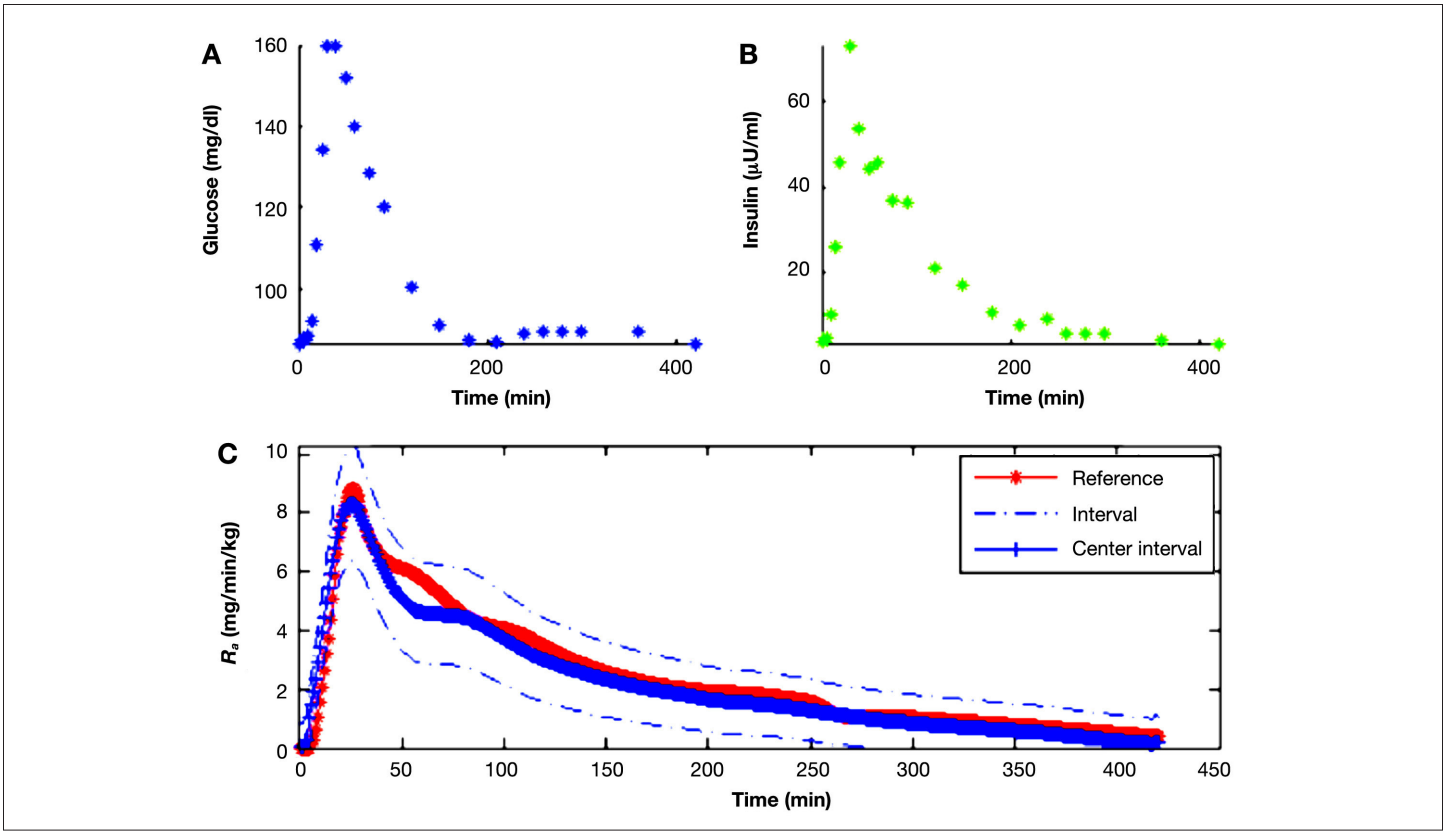

Figure 4. Interval R_a estimation for study one **(C)**, plasma glucose **(A)**, and plasma insulin **(B)**.

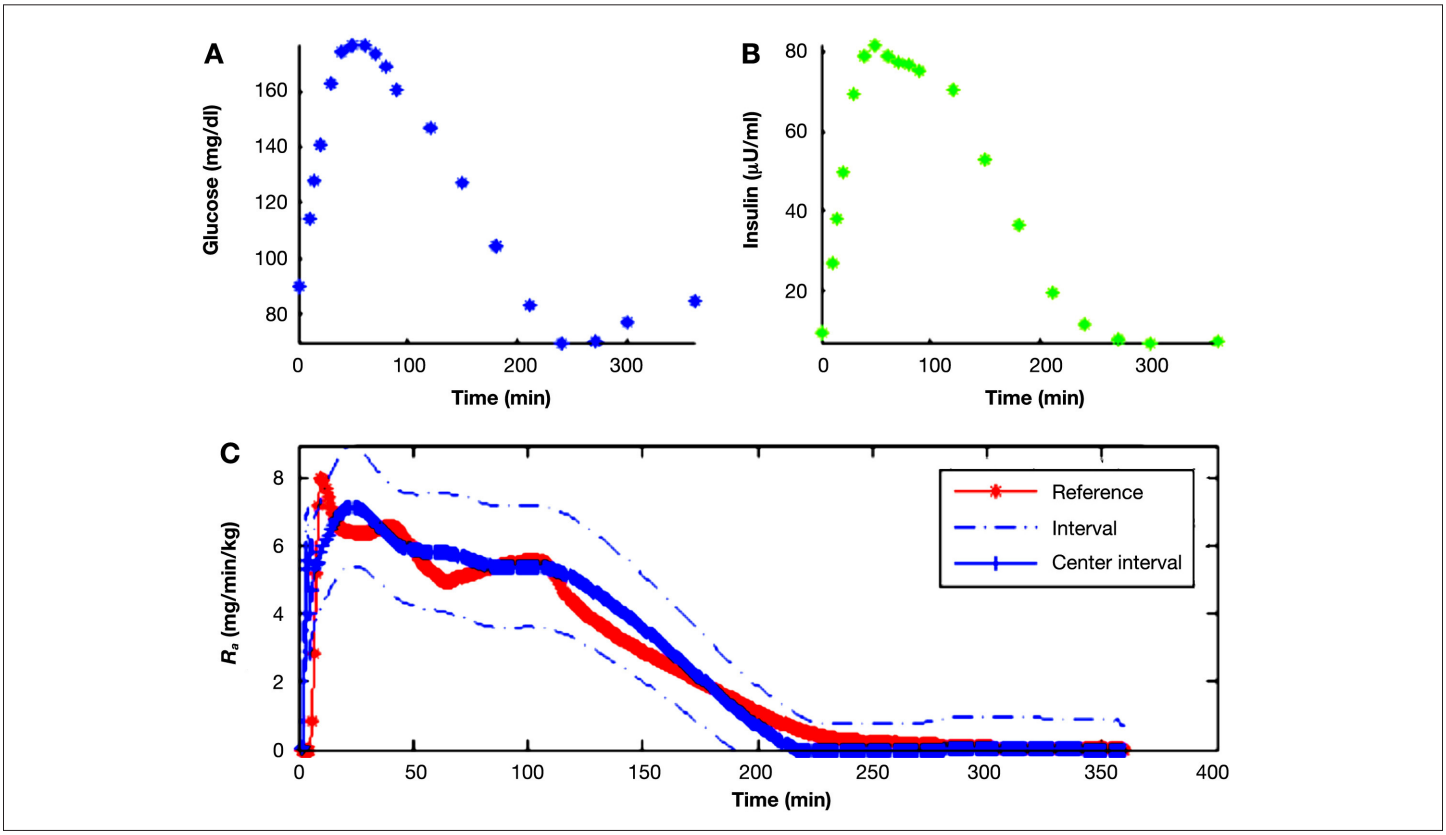

Figure 5. Interval R_a estimation for study one **(C)**, plasma glucose **(A)**, and plasma insulin **(B)**.

While multitracer protocols will remain the gold standard for estimating R_a, our proposed method is a good alternative when multitracer-based studies are not feasible.

One of the key points of the proposed technique is the fact that it only requires the identification of one parameter of the minimal model, while the rest of the parameters can be considered to vary inside relatively small ranges. This characteristic makes the parameter identification process very simple as no identifiability problems are present. To test this hypothesis, interval analysis, a well-established technique for robust analysis, was employed. For this purpose, uncertainty was carefully selected based on earlier studies on the variability of such parameters as well as technical specifications of the different employed measurement techniques.

This method has been proven to be sound because the obtained R_a interval estimate includes the reference one. Furthermore, and more importantly, the method is accurate because the center of such an interval estimate correlates well with the reference value.

Concerning the new technique for estimating S_I, it highly correlates with an existing clinically validated technique. Despite both methods seeming to be equivalent, the proposed technique is methodologically more robust since it does not require any *a priori* assumption on R_a.

In addition to its application to large clinical studies for the evaluation of the role of R_a in patients with impairments in glucose metabolism, the technique presented is being applied to build a model library of mixed meals using data from the literature. This library could be incorporated into existing T1DM simulators in order to account for more realistic and varied meals. Furthermore, it could be used in an artificial pancreas context by any algorithm that requires robust glucose estimates such as robust fault detection algorithms, which detect faults on the glucose sensors and insulin pumps, or a robust model-based glucose controller.

Conclusions

Existing techniques for estimating the rate of glucose appearance (R_a) from a mixed meal are either experimentally complex (i.e., multitracer protocols) or numerically complex (e.g., Bayesian estimation). In this article, a simple method, based on the glucose-insulin minimal model has been proven to be an alternative effective way to estimate R_a.

In summary, a new technique for estimation of the rate of glucose appearance is described, only requiring the identification of insulin sensitivity (S_I) from the minimal model, with the remaining parameters fixed to mean population value. By using interval analysis, a robust estimate of R_a represented by a band including all possible behaviors is obtained, and in *in-silico* trials, it has been proven that the robust estimate obtained contains the reference behavior. Furthermore, the center of the interval estimate is highly correlated with the reference.

A new technique for estimating S_I, which unlike earlier methods, does not require any assumption on R_a, has been presented and validated.

Finally, this new technique showed excellent results when tested with actual clinical data.

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