A System Model of Oral Glucose Absorption: Validation on Gold Standard Data

Chiara Dalla Man, Michael Camilleri, and Claudio Cobelli*, *Fellow, IEEE*

***Abstract*—A reliable model of glucose absorption after oral ingestion may facilitate simulation as well as pathophysiological studies. One of the difficulties for the development and quality assessment of such models has been the lack of gold standard data for their validation. Thus, while data on plasma concentrations of glucose are available, the rates of appearance in plasma of ingested glucose (Ra) were not available to develop such models. Here we utilize the recent availability of Ra data, estimated with a model-independent multiple tracer technique, to formulate a system model of intestinal glucose absorption. Two published and two new models are tested on this new data set. One of the two new models performed best: it is nonlinear, describes the Ra data well and its parameters are estimated with good precision. This model has important potential both in simulation contexts, e.g., it can be incorporated in whole-body models of the glucose regulatory system, as well as in physiological and clinical studies to quantitatively characterize possible impairment of glucose absorption in particular populations such as elderly and diabetic individuals.**

***Index Terms*—Gastric emptying, gastrointestinal system, meal, OGTT, parameter estimation, physiological model.**

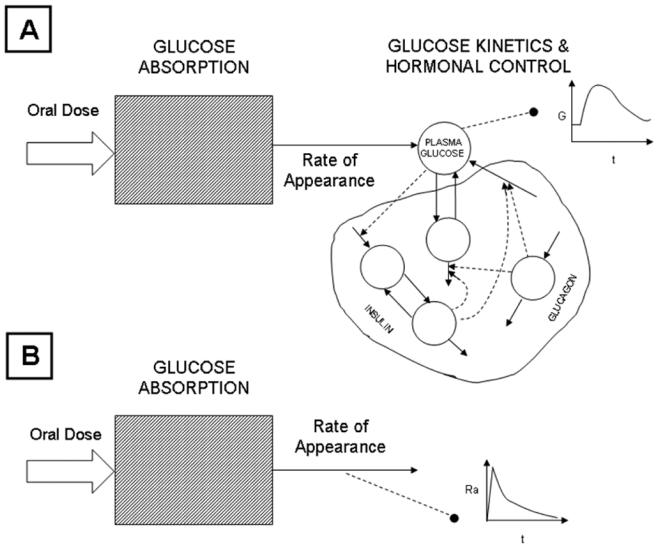

Fig. 1. (A) Glucose absorption modeling in absence of gold standard Ra data. (B) Glucose absorption modeling in presence of gold standard Ra data.

I. Introduction

ORAL ingestion of glucose is used in everyday meals as well as in the most important clinical test to assess glucose tolerance in humans, through the oral glucose tolerance test (OGTT). After ingestion, glucose is absorbed in the upper gastrointestinal tract, transported to the splanchnic bed (mostly the liver) and, finally, reaches the peripheral circulation. We have recently proposed a model of glucose absorption [1], [2], which describes the rate of glucose appearance in the peripheral circulation through a series of linear functions. However a model describing or mimicking the mechanisms of glucose transit through the gastrointestinal tract, would be very useful to study possible abnormalities of glucose absorption in particular populations, e.g., elderly versus young and diabetic versus normal individuals, as well as validating simulation models of glucose regulation. In fact, only a few of the currently available simulation models allow an oral route of glucose administration [3]–[6] but in all, the glucose absorption process is described rather simplistically. Modeling glucose absorption after oral ingestion has been difficult because of lack of gold standard validation data. In fact, if such a model is tested only on plasma glucose concentrations, there is the need to append to the glucose absorption model a whole-body model of glucose kinetics and their hormonal control [Fig. 1(A)]. Under such assumptions, model error compensations are likely to occur and yet go undetected. This is because a good fit of the plasma glucose concentration can easily mask possible model errors in the glucose absorption, as these errors are compensated by errors in the whole-body description of glucose kinetics.

The gold standard data to test a glucose absorption model would be provided by detailed knowledge of the time course of appearance in plasma of ingested glucose (Ra). This would allow avoidance of the model of whole-body glucose kinetics [Fig. 1(B)]. However, reliable model-independent knowledge of Ra requires the use of multiple tracer, oral glucose protocols implementing the tracer-to-tracee ratio clamp technique [7].

Only recently have these data become available [7], [8] and have been utilized in this study. Thus, the aim is to propose and validate a new glucose absorption model based on the reported glucose appearance (Ra) data that are used as the gold standard. Two published models [3], [9] are tested on this new validation data set and two new models, one linear and one nonlinear, are proposed. In fact, many authors agree [10]–[17] that the gastric emptying of liquids occurs exponentially and depends on the size of the meal, its energy density and the amount of nutrient in the stomach. On the other hand, with increasing nutrient and

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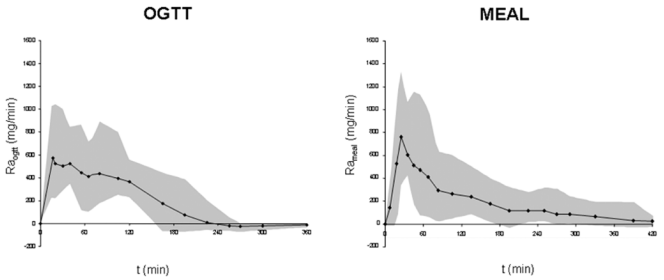

Fig. 2. Rate of appearance (Ra) measured with the multiple tracer tracer-to-tracee clamp technique during OGTT (left) and meal (right); grey area represents range of variability.

caloric content of the liquid phase of the meal, there is a deceleration from the exponential model and closer approximation to linearity. Thus, linear emptying is a characteristic of fully homogenized solids and the compositions of oral food used in typical studies of postprandial glycemia, where the glucose is usually in a liquid form are likely not emptied linearly. This well-known physiological principle was, thus, incorporated into one of the two new models.

II. Data

The database consists of 41 subjects with different levels of glucose tolerance: 21 of the participants ($\text{age} = 41 \pm 1$ years, $\text{BMI} = 27 \pm 1\ \text{kg/m}^2$) underwent a labeled OGTT and 20 ($\text{age} = 49 \pm 5$ years, $\text{BMI} = 26 \pm 1\ \text{kg/m}^2$) a labeled mixed meal.

The OGTT entails oral administration of 75 g of glucose at time zero (71 g unlabelled glucose, 4 g $[\text{U}^{13}\text{-C}_6]$-glucose tracer) [8]. At time zero, $[^2\text{H}_2]$-glucose was also infused intravenously at a variable rate to mimic the anticipated rate of appearance of the ingested glucose. Blood samples were collected at time -15, 0, 10, 15, 20, 30, 40, 50, 60, 70, 80, 90, 120, 150, 180, 210, 240, 270, 300, and 360 min and plasma glucose and tracer glucose concentrations measured. Since the plasma tracer-to-tracee ratio $[^2\text{H}_2]$-glucose/$[\text{U}^{13}\text{-C}_6]$-glucose (TTR) was maintained virtually constant, an essentially model-independent oral glucose rate of appearance (Ra_{ogtt}) was reconstructed [8] [Fig. 2 (left)]. Some small negative values, particularly in the last 100 min of Ra_{ogtt}, can be noted. The tracer-to-tracee clamp technique is certainly the state of art method to estimate Ra, but it is not possible to maintain TTR perfectly constant throughout the experiment. Thus, some variation of TTR occurred in the last 100 min of the OGTT (see [8, Fig. 3]). However, negative Ra values are very small and, since they occur in the last portion of the experiment when the absorption process is most certainly concluded, one can safely assume that they are not different from zero.

The mixed meal (10 kcal/kg, 45% carbohydrate, 15% protein, 40% fat, 90 ± 5 g of glucose) was labeled with [1-^{13}C]-glucose [7]. Beginning at time zero, [6-^{3}H]-glucose was infused intravenously at a variable rate in order to mimic the anticipated rate of appearance of the ingested meal. Plasma samples were collected at -120, -30, -20, -10, 0, 5, 10, 15, 20, 30, 40, 50, 60, 75, 90, 120, 150, 180, 210, 240, 260, 280, 300, 360, and 420 min and plasma glucose and tracer glucose concentrations measured. Since the plasma tracer-to-tracee ratio [6-^{3}H]-glucose/[1-^{13}C]-glucose was maintained virtually constant, a model-independent estimate of meal glucose rate of appearance (Ra_{meal}) was reconstructed [7] [Fig. 2(right)].

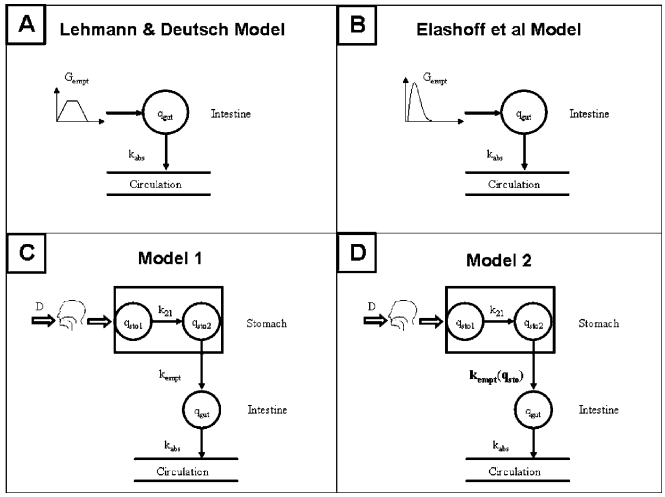

Fig. 3. (A) Lehmann and Deutsch model [3], which assumes a trapezoidal gastric empting function (G_{empt}), a single compartment for the intestine (q_{gut}) and a constant rate of intestinal absorption (k_{abs}). (B) Elashoff *et al.* model [11], which assumes a power exponential gastric empting function (G_{empt}), a single compartment for the intestine (q_{gut}) and a constant rate of intestinal absorption (k_{abs}). (C) Model 1, which assumes two compartments for the stomach (one for the liquid and one for the solid phase) a constant gastric empting rate (k_{empt}), a single compartment for the intestine (q_{gut}) and a constant rate of intestinal absorption (k_{abs}). (D) Model 2, which assumes two compartments for the stomach (one for the liquid and one for the solid phase) a gastric empting rate (k_{empt}) dependent on the total amount of glucose in the stomach (q_{sto}), a single compartment for the intestine (q_{gut}) and a constant rate of intestinal absorption (k_{abs}).

III. Models

A few models are available to interpret the rate of appearance of glucose in plasma. One is that by Lehmann and Deutsch present in AIDA [3] as well as in other simulators [6]. Another one is the power exponential model by Elashoff *et al.* [9]. Both these models will be briefly presented (for more details we refer to the original references). In addition, two new models will be proposed.

A. Lehmann and Deutsch Model

This model describes glucose absorption by the gut as shown in Fig. 3(A). It assumes that gastric emptying is a trapezoidal function and that intestinal absorption follows first order linear kinetics. Model equations are

$$\begin{cases} \dot{q}_{\text{gut}}(t) = -k_{\text{abs}} \cdot q_{\text{gut}}(t) + G_{\text{empt}}(t) \\ Ra(t) = f \cdot k_{\text{abs}} \cdot q_{\text{gut}}(t) \end{cases} \tag{1}$$

where q_{gut} is the amount of glucose in the gut, k_{abs} is the rate constant of intestinal absorption and f is the fraction of the intestinal absorption which actually appears in plasma. Parameter f was not present in the original model [3], but it was introduced to perform a proper comparison with the other models (it

is a scale factor and does not affect the shape of the estimated profile). This fraction (f) is calculated in each individual from $\mathrm{Ra}_{\mathrm{ogtt/meal}}$ data as:

$$f = \frac{\int_0^\infty \mathrm{Ra}_{\mathrm{ogtt/meal}}(t)}{D} \tag{2}$$

$G_{\mathrm{empt}}(t)$ is the gastric emptying and is described by: See equation (3) at the bottom of the page where

$$V_{\max} = \frac{2 \cdot D}{T_{\mathrm{up}} + 2 \cdot T_{\max} + T_{\mathrm{down}}} \tag{4}$$

is the maximum velocity of gastric emptying, D is the ingested glucose dose, T_{up}, $T_{\max}$ and T_{down} are the duration of rising up, staying and dropping periods of $G_{\mathrm{empt}}(t)$, respectively.

B. Elashoff Model

This model is still described by (1) but a different description for $G_{\mathrm{empt}}(t)$ is postulated. It is assumed that the fraction of glucose in the duodenum increases following a power exponential function [Fig. 3(upper-right)]

$$q_{\mathrm{duo}}(t) = D \cdot \{1 - e^{\{-(kt)^\beta\}}\} \tag{5}$$

where k is the rate of emptying and β a shape factor and, thus, the gastric empting rate is

$$G_{\mathrm{empt}}(t) = \dot{q}_{\mathrm{duo}}(t) = D \cdot \beta \cdot k^\beta \cdot t^{\beta-1} \cdot e^{\{-(kt)^\beta\}}. \tag{6}$$

C. Model 1

This model describes glucose transit through the stomach and upper small intestine as a linear chain of three compartments, the first two representing the stomach (solid and liquid phase), the third one representing the intestine [Fig. 3(C)]. Model equations are

$$\begin{cases} \dot{q}_{\mathrm{sto1}}(t) = -k_{21} \cdot q_{\mathrm{sto1}}(t) + D\delta(t) \\ \dot{q}_{\mathrm{sto2}}(t) = -k_{\mathrm{empt}} \cdot q_{\mathrm{sto2}}(t) + k_{21} \cdot q_{\mathrm{sto1}}(t) \\ \dot{q}_{\mathrm{gut}}(t) = -k_{\mathrm{abs}} \cdot q_{\mathrm{gut}}(t) + k_{\mathrm{empt}} \cdot q_{\mathrm{sto2}}(t) \\ Ra(t) = f \cdot k_{\mathrm{abs}} \cdot q_{\mathrm{gut}}(t) \end{cases} \tag{7}$$

where q_{sto1} and q_{sto2} are the amounts of glucose in the stomach (solid and liquid phase, respectively), $\delta(t)$ is the impulse function, D is the amount of ingested glucose, q_{gut} is the glucose mass in the intestine, k_{21} the rate of grinding, k_{empt} the rate of gastric emptying, k_{abs} the rate constant of intestinal absorption, and f the fraction of the intestinal absorption which actually appears in plasma (2).

D. Model 2

All the above models failed in fitting $\mathrm{Ra}_{\mathrm{meal}}$ and $\mathrm{Ra}_{\mathrm{ogtt}}$ satisfactorily (see Results). The reason is likely their simplistic structure relative to the complexity of the Ra signal. It is, in fact, well known, for instance, that the gastric emptying of liquids depends nonlinearly on the size of the meal, its energy density and the amount of nutrient in the stomach [10]–[13]. Moreover gastric emptying is described as a biphasic process in many studies [12], [14]. This nonlinear behavior is also confirmed by our data. We note two phases in $\mathrm{Ra}_{\mathrm{meal}}$ [Fig. 2(right)] and even three phases in $\mathrm{Ra}_{\mathrm{ogtt}}$ [Fig. 2(left)]. Clearly, a linear model does not capture these features. We, thus, moved to a nonlinear model based on available knowledge on gastric emptying and glucose absorption [Fig. 3(D)]. In such a model, the stomach is represented by two compartments (one for the solid and one for the triturated phase of the meal) while one compartment is used to describe the gut, that is, the part of the digestive tract beyond the stomach. Model equations are the same as presented above for the linear model (7), except for the empting rate k_{empt}, which is no longer constant but depends on the total amount of glucose in the stomach q_{sto} [10]–[13], [15]–[17] as follows:

$$k_{\mathrm{empt}}(q_{\mathrm{sto}}) = k_{\min} + \frac{k_{\max} - k_{\min}}{2} \cdot \{\tanh[\alpha(q_{\mathrm{sto}} - b \cdot D)] - \tanh[\beta(q_{\mathrm{sto}} - c \cdot D)] + 2\} \tag{8}$$

with

$$q_{\mathrm{sto}}(t) = q_{\mathrm{sto1}}(t) + q_{\mathrm{sto2}}(t) \tag{9}$$

A better grasp of the parametric control of q_{sto} on k_{empt} can be obtained by its graphical representation (Fig. 4): k_{empt} is maximum $(= k_{\max})$ when the stomach contains the amount of the ingested glucose D, i.e at the beginning of the experiment, then it decreases with a rate α to a minimum, $k_{\min}$, then it recovers back again to its maximum $k_{\max}$ with a rate β. b is the percentage of the dose for which k_{empt} decreases at $(k_{\max} - k_{\min})/2$ and corresponds to the flex point of the curve. Similarly c is the percentage of the dose for which k_{empt} is back to $(k_{\max} - k_{\min})/2$ and corresponds to the flex of the recovery portion. Parameters α and β are constrained by imposing that $k_{\mathrm{empt}} = k_{\max}$ for both $q_{\mathrm{sto}} = D$ and $q_{\mathrm{sto}} = 0$

$$\alpha = \frac{5}{2 \cdot D \cdot (1 - b)} \tag{10}$$

$$\beta = \frac{5}{2 \cdot D \cdot c}. \tag{11}$$

If c is small, k_{empt} remains at level $k_{\min}$ till the stomach is completely empty and (8) simplifies as

$$k_{\mathrm{empt}}(q_{\mathrm{sto}}) = k_{\min} + \frac{k_{\max} - k_{\min}}{2} \cdot \{\tanh[\alpha(q_{\mathrm{sto}} - b \cdot D)] + 1\}. \tag{12}$$

$$G_{\mathrm{empt}}(t) = \begin{cases} \frac{V_{\max}}{T_{\mathrm{up}}} \cdot t, & t < T_{\mathrm{up}} \\ V_{\max}, & T_{\mathrm{up}} \le t < T_{\mathrm{up}} + T_{\max} \\ V_{\max} - \frac{V_{\max}}{T_{\mathrm{down}}} \cdot (t - T_{\mathrm{up}} - T_{\max}), & T_{\mathrm{up}} + T_{\max} \le t < T_{\mathrm{up}} + T_{\max} + T_{\mathrm{down}} \\ 0, & \text{otherwise} \end{cases} \tag{3}$$

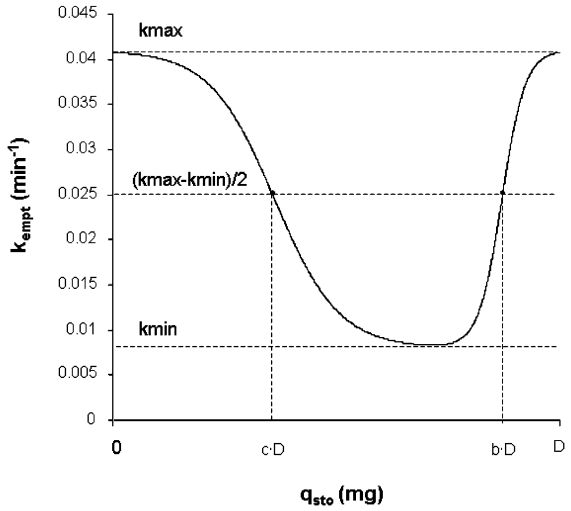

Fig. 4. Qualitative plot of gastric emptying rate ($k_{\rm empt}$) as function of the amount of glucose in the stomach $q_{\rm sto}$: it equals $k_{\max}$ when the stomach contains the amount of the ingested glucose, D, then it decreases to a minimum ($k_{\min}$). b is the percentage of the dose for which $k_{\rm empt}$ decreases at $(k_{\max} - k_{\min})/2$; c is the percentage of the dose for which $k_{\rm empt}$ is back to $(k_{\max} - k_{\min})/2$.

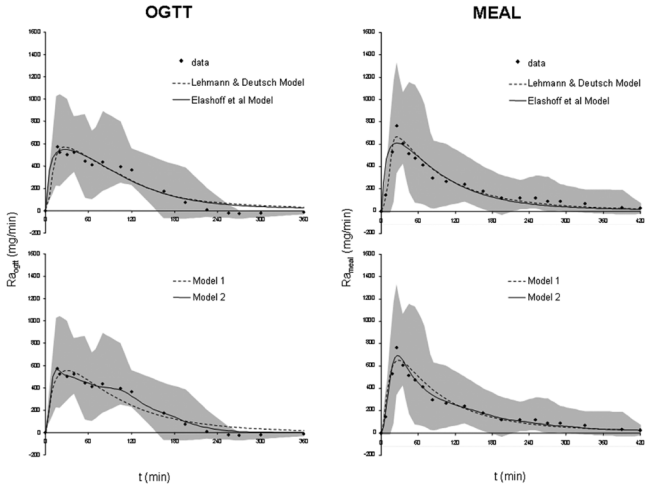

Fig. 5. Upper panel: data (♦) versus predictions during OGTT (right) and meal (left) of Lehmann and Deutsch (broken line) and Elashoff *et al.* (solid line) Models. Lower panel: data (♦) versus predictions during OGTT (right) and meal (left) of Model 1 (broken line) and Model 2 (solid line).

IV. Identification

A. A Priori Identifiability

All the models are *a priori* uniquely identifiable [18], [19] except Model 1 which is nonuniquely identifiable and there are six possible solutions for the parameter vector $[k_{21}\ k_{\rm empt}\ k_{\rm abs}]$, one for each permutation of its elements. Thus, additional assumptions were needed to make the model uniquely identifiable. We assumed $k_{21} = k_{\rm empt}$ and chose, out of the two possible solutions, the one which guarantees $k_{\rm empt} > k_{\rm abs}$.

B. Parameter Estimation

All models were numerically identified by nonlinear least squares [18], [19] as implemented in SAAM II software [20]. Measurement error on Ra was assumed independent Gaussian with zero mean and unknown constant standard deviation (estimated *a posteriori*); negative values of Ra were not considered in the optimization process. To favour numerical identifiability of Model 2, especially in the meal studies, the constraint $k_{21} = k_{\max}$ was imposed.

C. Statistical Analysis

Data are presented as mean ± SE. Unpaired comparisons were done by Mann-Whitney rank test with significance level at $\alpha = 0.05$ [21].

V. Results

A. Lehmann and Deutsch Model

The model was not able to fit satisfactorily $\rm Ra_{ogtt}$ and $\rm Ra_{meal}$ profiles: average model prediction is plotted against Ra measurements in Fig. 5 (upper panels, broken line) for both OGTT and meal. The mean sum of squared residual (RSS) was 173363 and 185369 for the OGTT and meal, respectively. Parameters were estimated with poor precision: $T_{\rm up}^{\rm OGTT} = 9.37 \pm 1.59$ min (mean CV = 198%); $T_{\rm down}^{\rm OGTT} = 27.81 \pm 9.90$ min (122%); $T_{\max}^{\rm OGTT} = 6.44 \pm 4.74$ min (32%) but in 19 subjects it collapsed to zero; $k_{\rm abs}^{\rm OGTT} = 0.018 \pm 0.005\ \rm min^{-1}$ (18%); $T_{\rm up}^{\rm MEAL} = 16.35 \pm 1.63$ min (23%); $T_{\rm down}^{\rm MEAL} = 9.00 \pm 3.12$ min (495%); $T_{\max}^{\rm MEAL}$ collapsed to zero in all subjects; $k_{\rm abs}^{\rm MEAL} = 0.011 \pm 0.001\ \rm min^{-1}$ (12%).

B. Elashoff Model

The model was not able to fit satisfactorily $\rm Ra_{ogtt}$ and $\rm Ra_{meal}$ profiles: average model prediction is plotted against Ra measurements in Fig. 5 (upper panels, solid line) for both OGTT and meal. Mean RSS was 180286 and 217213 for the OGTT and meal, respectively. Parameters estimates are: $\beta^{\rm OGTT} = 1.23 \pm 0.06$ (23%); $k^{\rm OGTT} = 0.011 \pm 0.001\ \rm min^{-1}$ (19%); $k_{\rm abs}^{\rm OGTT} = 0.231 \pm 0.017\ \rm min^{-1}$ (185%); $\beta^{\rm MEAL} = 1.03 \pm 0.05$ (53%); $k^{\rm MEAL} = 0.015 \pm 0.003\ \rm min^{-1}$ (50%); $k_{\rm abs}^{\rm MEAL} = 0.198 \pm 0.074\ \rm min^{-1}$ (419%).

C. Model 1

The linear model was not able to fit satisfactorily Raogtt and Rameal profiles: average model prediction is plotted against Ra measurements in Fig. 5 (lower panel, broken line) for both OGTT and meal. Mean RSS was 195267 and 223897 for the OGTT and meal, respectively. Parameters were estimated with good precision: $k_{\rm empt}^{\rm OGTT} = 0.222 \pm 0.037\ \rm min^{-1}$ (76%); $k_{\rm abs}^{\rm OGTT} = 0.013 \pm 0.001\ \rm min^{-1}$ (36%); $k_{\rm empt}^{\rm MEAL} = 0.180 \pm 0.021\ \rm min^{-1}$ (50%); $k_{\rm abs}^{\rm MEAL} = 0.012 \pm 0.001\ \rm min^{-1}$ (12%).

D. Model 2

The nonlinear model fitted $\rm Ra_{ogtt}$ and $\rm Ra_{meal}$ profiles very well both in average as well as in each individual (not shown) in spite of the large interpatient variability of the glucose absorption profile. Average model prediction is plotted against Ra measurements in Fig. 5 (lower panels, solid line) for both OGTT

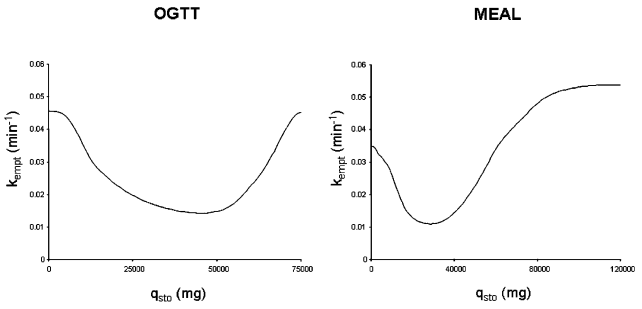

Fig. 6. Average gastric emptying rate estimated during OGTT (left) and meal (right) as function of the amount of glucose in the stomach. During meal (12) instead of (8) was employed in ten subjects and in those cases $k_{\rm empt} = k_{\rm min}$ when $q_{\rm sto} = 0$; this causes that on average, for $q_{\rm sto} = 0$, $k_{\rm empt}$ is different from $k_{\rm max}$.

and meal. Mean RSS was 74781 and 123713 for the OGTT and meal, respectively, both significantly lower ($p < 0.00001$ and $p < 0.005$) than those obtained with the other models. Parameter estimates are: $k_{\rm max}^{\rm OGTT} = 0.045 \pm 0.004$ min^{-1} (23%); $k_{\rm min}^{\rm OGTT} = 0.013 \pm 0.002$ min^{-1} (13%); $k_{\rm abs}^{\rm OGTT} = 0.205 \pm 0.022$ min^{-1} (56%); $b^{\rm OGTT} = 0.85 \pm 0.02$ (4%); $c^{\rm OGTT} = 0.25 \pm 0.03$ (19%); $k_{\rm max}^{\rm MEAL} = 0.054 \pm 0.009$ min^{-1} (26%); $k_{\rm min}^{\rm MEAL} = 0.006 \pm 0.001$ min^{-1} (41%); $k_{\rm abs}^{\rm MEAL} = 0.071 \pm 0.006$ min^{-1} (46%); $b^{\rm MEAL} = 0.69 \pm 0.03$ (6%). Parameter $c^{\rm MEAL}$ was virtually zero in ten subjects and, thus, (12) instead of (8) was employed; in the remaining subjects $c^{\rm MEAL} = 0.17 \pm 0.02$ (25%).

By comparing model parameters estimated during OGTT and meal, Model 2 predicts a similar maximum gastric empting rate ($k_{\rm max}^{\rm OGTT} = 0.045 \pm 0.004$ versus $k_{\rm max}^{\rm MEAL} = 0.054 \pm 0.009$, not significantly different) but lower minimum gastric empting rate, absorption rate and fraction b in meal than in OGTT ($k_{\rm min}^{\rm OGTT} = 0.013 \pm 0.002$ versus $k_{\rm min}^{\rm MEAL} = 0.006 \pm 0.001$, $p < 0.001$; $k_{\rm abs}^{\rm OGTT} = 0.205 \pm 0.022$ versus $k_{\rm abs}^{\rm MEAL} = 0.071 \pm 0.006$, $p < 0.001$; $b^{\rm OGTT} = 0.85 \pm 0.02$ versus $b^{\rm MEAL} = 0.69 \pm 0.03$, $p < 0.001$; c is not different in the two tests. As a result gastric emptying rate $(k_{\rm empt})$ as function of $q_{\rm sto}$ are different between the two tests (Fig. 6). It is important to note that, when during meal (12) is used instead of (8), one has $k_{\rm empt} = k_{\rm min}$ when $q_{\rm sto} = 0$. As a result, on average, for $q_{\rm sto} = 0$, $k_{\rm empt}$ is different from $k_{\rm max}$.

VI. Discussion

A reliable model describing glucose traversing through the gastrointestinal tract (esophagus, stomach, intestine), splanchnic bed and its appearance in the peripheral circulation could be very useful in to assess impairment of glucose absorption e.g., in elderly and diabetic individuals. Alternatively, it could be integrated in a glucose homeostasis simulator to predict plasma glucose and insulin concentrations after oral glucose intake. The aim of this study was, thus, to formulate a system model of the glucose rate of appearance in plasma after an oral glucose load and validate it against gold standard data, i.e., glucose rate of appearance in plasma measured with the multiple tracer-to-tracee ratio technique both during OGTT and meal [7], [8], [22] in a virtually model-independent way. In fact, testing the model on these Ra gold standard data instead of plasma glucose concentration avoids the need to append to the glucose absorption model a whole-body model of glucose kinetics and their hormonal control (Fig. 1), thus avoiding possible model error compensation.

In this paper, two new models were proposed to mimic glucose transport and appearance in the peripheral circulation in humans: one linear (Model 1) and one nonlinear (Model 2), each of which consisted of a chain of three compartments, the first two representing the stomach (solid and triturated phase), the third one representing the intestine [Fig. 3(C) and (D)]. They both assumed a constant rate of intestinal absorption $(k_{\rm abs})$ but were differentiated by the assumptions in the description of the gastric emptying rate, which was constant for the linear model, and dependent on the total amount of glucose in the stomach for the nonlinear model. As discussed in the introduction, gastric emptying of liquids is a nonlinear function of the amount of nutrient in the stomach, especially with different composition or physical nature of the meals, ranging from fully homogenized solids to liquids, which were the oral meals used in this study. Our results with model 1, which describes gastric emptying as a linear process, support the principles summarized above since the model is not able to accurately describe the data (Fig. 5, bottom panels, broken line). On the contrary, model 2 showed a very good fit of both OGTT (liquid meal) and homogenized meal Ra data (Fig. 5 lower panels, solid line; sum of squared residuals significantly lower with model 2 than with all other models, both during OGTT, $p < 0.00001$, and meal, $p < 0.005$). We also tested two published models [3], [9] which were less accurate in fitting $\rm Ra_{ogtt/meal}$ and showed either systematic overestimation or underestimation of Ra. Moreover, neither of the published models provided good precision in the parameter estimates, while parameters of Model 1 and 2 proposed by our study were estimated with reasonable precision. We surmise that the published models' failure was related to their reliance on relatively simplistic model structures which cannot capture the complexity of the Ra signal, for instance the three different phases showed by $\rm Ra_{ogtt}$ and the two phases evident in $\rm Ra_{meal}$ (Fig. 2). Conversely, the nonlinearity introduced in the gastric emptying rate, besides being a more realistic description of glucose transit from the stomach to the duodenum based on scintigraphic quantitation in the literature, also allows to better fit a variety of $\rm Ra_{ogtt/meal}$ curves. From these considerations, one concludes that Model 2 is better suited to describe glucose transit through the gastrointestinal tract.

An interesting feature of Model 2 is that its parameters are potentially usable to quantitatively characterize the different Ra patterns observed in various conditions, e.g., young *vs* elderly subjects, men *vs* women, diabetic *vs* nondiabetic subjects. These studies are currently underway (see [22], [23]), but one can appreciate the potential to use the model by observing the different parameters that characterize Ra after an OGTT or a meal. Ra presents different profiles: during OGTT absorption shows three different phases (Fig. 2), a peak in the first 30 min, a plateau till approximately $t = 120$ min and a rapid decrease to zero in the last part; conversely during the homogenized meal, the first peak is at $t = 60$ min (reflecting the slower emptying of solids compared to liquids), then the curve decreases to zero without showing a plateau. These qualitative features of the curves are

quantitatively characterized by the model: the maximum gastric empting rate is similar during the two test meals, while both minimum gastric empting rate $k_{\min}$, absorption rate $k_{\rm abs}$ and fractions b and c are lower in the meal study than in the OGTT (Fig. 6). This agrees with the knowledge that glucose absorption is slower during a mixed meal than during an OGTT due to the presence of other nutrients, mainly fats, which significantly slow down gastric digestion $\left(k_{\min}^{\rm MEAL} < k_{\min}^{\rm OGTT}\right)$ and intestinal absorption $\left(k_{\rm abs}^{\rm MEAL} < k_{\rm abs}^{\rm OGTT}\right)$.

We perceive that this new system model will also prove useful when integrated into whole-body glucose homeostasis simulators. Given the great demand of normal life, whole-body glucose system simulators, in order to better design diabetic therapeutic regimens and to provide a test bed for new closed loop algorithms and glucose sensors, we anticipate an interest in this model and we plan to incorporate it into our simulator which is currently in its final stage of development [24]

In conclusion, the availability of $\rm Ra_{meal}$ and $\rm Ra_{ogtt}$ gold standard data has allowed us to formulate a new model of glucose rate appearance after an oral glucose intake which well predicts measured profiles, provides easily interpretable parameters and has great potential to be incorporated in normal life, glucose system simulators as well as to quantitatively characterize glucose absorption in different groups, such as the elderly and diabetic populations.

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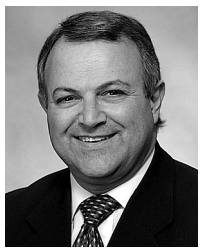

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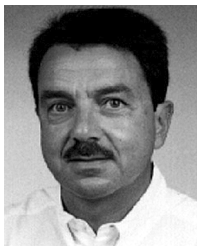

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