Modeling Intestinal Glucose Absorption from D-Xylose Data

Danilo Dursoniah[1][a], Maxime Folschette[1][b], Rebecca Goutchtat[2], Violeta Raverdy[2], François Pattou[2] and Cédric Lhoussaine[1][c]

[1]*Univ. Lille, CNRS, Centrale Lille, UMR 9189 CRIStAL, F-59000 Lille, France*

[2]*Univ. Lille, Inserm, CHU Lille, U1190 - EGID,F-59000 Lille, France*

danilo.dursoniah@univ-lille.fr, maxime.folschette@centrale-lille.fr, rebecca.goutchtat@inserm.fr,
{violeta.raverdy, francois.pattou, cedric.lhoussaine}@univ-lille.fr

Keywords: Systems Biology, Diabetes, Parameters Estimation, Practical Identifiability, Sensitivity Analysis.

Abstract: Type 2 Diabetes (T2D) is one of the main epidemics of this century. One of the hypothesis of medical research is that an important cause of T2D may be the abnormal regulation of intestinal glucose absorption (IGA). Early detection of IGA disorders, and, more generally, precision medicine, may help to prevent the risk of T2D. This could be achieved by predictive models of glucose dynamics in blood following an oral ingestion. Even though many such models have been proposed, they either do not cope with IGA at all, or their calibration requires the use of complex and invasive tracer protocols that make them clinically unusable on a daily basis. To overcome this issue, D-xylose may be used as an IGA marker. Indeed, it is a glucose analogue with similar intestinal absorption mechanisms but, contrary to glucose, its dynamics in blood only results from gastric emptying, intestinal absorption and elimination by the kidney. In this paper, we investigate a model-based assessment of IGA based on D-xylose dynamics in blood after oral absorption. We show that a multi-compartment model of instestinal absorption can fit very well D-xylose data obtained from different experimental conditions and be a good qualitative estimate of IGA. Additionnally, because gastric emptying is a possible confounding factor with intestinal absorption, we explore the relative contribution of both mechanisms to the rate of D-xylose (and thus glucose) appearance in blood.

1 INTRODUCTION

Type 2 diabetes (*T2D*) is a metabolic disease, with a high prevalence worldwide, that remains a major public health issue in all countries. T2D is mainly characterized by a high blood glucose concentration with an abnormally low concentration of blood insulin, its down-regulator hormone secreted by the pancreas. It is commonly admitted that T2D is correlated with a low pancreatic activity and a reduced ability for the different tissues to absorb and use the glucose available in the blood. As it has multifactorial causes, associated with various comorbidities, such as obesity, the challenge to develop an actual therapy is still up to be tackled.

One of the markers of possible risks of T2D in patients is a change in the glycemic postprandial response (Bergman et al., 2018), that is, a modification of the dynamics over time of glucose concentration in the blood after a meal. It has been shown that one of the major contributors of this postprandial response is intestinal glucose absorption (*IGA*) (Tricò et al., 2019; Baud et al., 2016). Therefore, IGA monitoring would lead to a better prevention of T2D in patients at risk, improve the cure of patients affected, and more generally better understand the physiological mechanisms at work in this disease.

In this regard, modeling postprandial glucose dynamics in blood is crucial to predict how a change of IGA can affect the concentration of glucose in blood and to devise new diabetes markers. This requires, in particular, to model the *rate of appearance of exogenous glucose* (Ra_G), that is, the rate of glucose coming from the meal. However, calibrating such a model involves the experimental measure of this rate, which is a difficult challenge. Indeed, the direct measurement of Ra_G requires an access to the portal vein, which is generally hardly feasible and even impossible on humans. In addition, it cannot be deduced from other easily observable variables like the concentration of glucose in blood, because other mechanisms occur all

[a] https://orcid.org/0009-0007-6159-1966
[b] https://orcid.org/0000-0002-3727-2320
[c] https://orcid.org/0000-0002-3970-3761

Dursoniah, D., Folschette, M., Goutchtat, R., Raverdy, V., Pattou, F. and Lhoussaine, C.
Modeling Intestinal Glucose Absorption from D-Xylose Data.
DOI: 10.5220/0012358300003657

In *Proceedings of the 17th International Joint Conference on Biomedical Engineering Systems and Technologies (BIOSTEC 2024) - Volume 1*, pages 438-445
ISBN: 978-989-758-688-0; ISSN: 2184-4305

the time: glucose excretion (by the kidneys), glucose production (by the liver) and metabolization (by the tissues), regulated by insulin.

The current approach to experimentally measure Ra_G is to perform oral glucose tests with multiple isotopic tracers that consist in ingesting labelled glucose (Toffolo et al., 2006). They allow to distinguish between the different fluxes of glucose in the blood, and to measure the fraction coming from the meal. Nevertheless, these tests are invasive and complex to set up in a clinical or lab routine, and as such don't allow to gather data on large cohorts of patients.

Here, we propose an alternative approach to measure Ra_G that uses D-xylose as an IGA marker. D-xylose is a sugar absorbed by the small intestine and eliminated by the kidneys, in the same way than glucose, but with no significant metabolization by any other organs, including the liver, unlike glucose. Therefore, as it is not stored, released, or regulated from an endogenous source, we can assume that monitoring D-xylose concentration in the blood mainly reflects its gastro-intestinal activity. Moreover, it is by far simpler to use than isotopic tracer methods. Using D-xylose as a quantitative marker of IGA in the clinical and experimental settings has already been proposed (Fujita et al., 1998; Baud et al., 2016; Goutchtat et al., 2022). However, such direct measurement is not perfectly accurate since it ignores the effect of D-xylose elimination that takes place in addition to intestinal absorption, and cannot distinguish the respective roles of gastric emptying and intestinal absorption in the rate of D-xylose appearance.

Related Works. So far, no mechanistic model of D-xylose dynamics has been proposed yet. When it comes to glucose dynamics, most of the models of glucose appearance in blood rely on a complex gastric emptying modeling. Historically, Elashoff et al. proposed the first well-referenced model to describe gastric emptying (Elashoff et al., 1982).

Later, Dalla Man et al. exposed the limitations of the previous approach from Elashoff et al., and proposed a complete gastro-intestinal model, not only describing the gastric emptying, but also the glucose intestinal absorption in post-prandial condition (Dalla Man et al., 2006). In this model, the intestinal absorption is reduced to a single flux with constant rate, whereas the gastric emptying involves a complex equation with 5 parameters. This model could fit their own dataset of exogenous glucose, obtained with the isotopic triple tracer method, considered as the gold standard experimental approach to measure Ra_G.

Salinari et al. proposed a spatial model of intestinal absorption and transit, defined by means of a system of partial differential equations, depending on time and on the position along the intestine (Salinari et al., 2011). The rate of transit was determined by their specific data, mainly depending on the length of the intestine (see Subsection 3.2). More importantly, in this spatial model, we can consider a non-uniform intestinal absorption rate along the intestine. This hypothesis is indeed considered as realistic and the authors show that different spatial distributions of absorption may result in different glucose appearance dynamics.

Contribution. In this paper, we propose a new model-based assessment of IGA. More precisely, we investigate a physiological model of D-xylose dynamics that is composed of multi-compartmental intestinal transit and absorption, and both exponential gastric emptying and D-xylose elimination. This model can be seen as a simplified and discretized version of the model of intestinal absorption by Salinari et al. While being simple, we show that our model can fit time series of D-xylose data obtained in different experimental conditions (oral and jejunal administration of D-Xylose) with a good accuracy and, most importantly, that it can predict Ra_G validated with tracer data. We also show that the rates of gastric emptying and of absorption, in particular, are identifiable.

In addition, to decypher the relative contribution of gastric emptying and intestinal absorption to D-xylose dynamics, we show that the alternative model of Dalla Man et al. (Dalla Man et al., 2006) emphasizying on gastric emptying cannot fit equally well our experimental data. Finally, we performed a sensitivity analysis to decypher which of the rate of gastric emptying and the rate of intestinal absorption have the most significant impact on the overall quantity of D-xylose absorbed after 180 minutes. We show that this quantity is more sensitive to intestinal absorption and that D-xylose can thus potentially serve as a marker of IGA that is easy to use in the clinical setting. All data and experiments are available at: https://zenodo.org/records/10136595.

2 MINIPIGS DATASETS

For our problematic, different experiments have been performed to monitor sugar in the blood after an intake of a bolus of sugar using intestinal or oral administration. This entails two subpopulations of pigs each producing several datasets.

The individuals of the first subpopulation underwent an oral and a jejunal administration. The *Oral bolus dataset* allows to monitor blood D-xylose in the

normal state after an oral administration of the meal. In the *Intestinal (or jejunal) bolus dataset* the stomach is bypassed and the meal is directly administrated in the small intestine. The blended meal includes 30 g of D-xylose.

The individuals of the second subpopulation underwent a surgical experiment (intestinal resection) to assess the sugar response in blood after a change in the absorption processes. This subpopulation is interesting to compare the rate of appearance of exogenous glucose (Ra_G) with the rate of appearance of D-xylose (Ra_X) in normal and experimental conditions to demonstrate the relevance of D-xylose to study IGA behavior. Indeed, this subpopulation benefitted from a gold standard technique to monitor their IGA, known as dual-tracer, implying two differently labeled glucoses to distinguish glucose from an exogenous source and glucose from an endogenous source (typically produced by the liver). This subpopulation thus produced four datasets: before and after the surgery, both measuring D-xylose and glucose concentrations in blood. The *Oral bolus before intestinal resection dataset* allows to monitor blood sugar in the normal state (before surgery) after an oral administration of the meal. In the *Oral bolus after intestinal resection dataset*, about 80% of the mid-part of the small intestine has been removed. After a time of recovery, an oral administration of the meal is performed. All these datasets are used to calibrate the models.

3 MODEL STRUCTURE AND CALIBRATION

This section presents the main model of this work and results provided by this model. The first step is to estimate the volume of distribution of D-xylose V_{D_X}, which represents the total volume of fluid that D-xylose can occupy once absorbed by the intestine: it serves as a reference to compute concentrations of D-xylose in the body instead of quantities. It is usually normalized by the body weight, so the dimension of V_{D_X} is dL/kg. After an intravenous injection experiment, it is defined by $V_{D_X} = \frac{D_X}{BW \cdot X_p}$ where D_X is the administrated dose of D-xylose (mg), X_p is the concentration of D-xylose in the blood (mg/dL) when D_X is fully administrated instantly, and BW is the body weight (kg).

From this work, we found a significant linear correlation (not shown) between the body weight and the volume of distribution.This observation allowed us to infer, from their body weight BW, the volume of distribution, denoted $V_{D_X}(BW)$, of the minipigs that did not underwent an intravenous injection experiment.

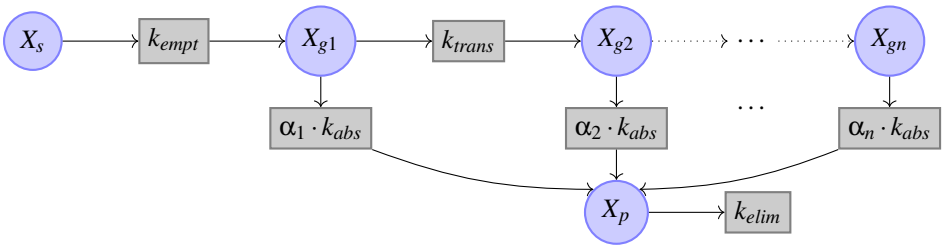
3.1 Multi-Compartment Model

The model that is used in the rest of this work is given in Figure 1 both as a system of ordinary differential equations (*ODEs*) and in the form of a reaction network (using a Petri net-like graphical notation). It is composed of the variables X_s (D-xylose in the stomach), X_p (D-xylose in the plasma), and $X_{g1}, \ldots, X_{gn}$ (D-xylose in the intestinal tract, where $n = 10$ for all following numerical analyses).

The rate k_{empt} (min^{-1}) models gastric emptying of the stomach into the intestine. This rate is willingly kept simple, as opposed to other modelings such as (Dalla Man et al., 2006) and as discussed in Section 4.2. Intestinal transit is modeled as a flux of D-xylose from each compartments X_{g_i} to the next, $X_{g_{i+1}}$. We assume that this flux is uniform with rate k_{trans} (min^{-1}) defined by $k_{trans} = \frac{1}{\tau}$ and $\tau = \frac{L}{u \cdot n}$ where τ is the time required for the transit through one compartment (min), L is the length of the small intestine (estimated at 1100 cm, the average length obtained from the surgery performed for the *oral bolus after resection dataset*), and u the speed of intestinal transit (empirically set to 6 cm/min, an estimation for the PDE intestinal model of (Salinari et al., 2011)).

The global intestinal absorption, from the gut to the plasma, is modeled with rate k_{abs} (min^{-1}). However, the distribution of this rate of absorption along the intestine is supposed non-uniform. For this, for each variable X_{g_i}, the rate of absorption is modulated by a strictly positive parameter α_i. The sum of all parameters α_1, ..., α_n equals 1, so that the global absorption rate (the sum of the rates from each compartment of the intestine) is thus k_{abs}. Note that if the distribution of these parameters is uniform (that is, $\alpha_i = 1/n$ for all i) then this model is equivalent to a model where the whole intestine would be represented by a unique variable X_g and an output rate of k_{abs}. We don't force any particular distribution, and the parameters α_i are estimated in the following.

Finally, here, "elimination" is a generic term to designate both D-xylose renal clearance and metabolization, both resulting in D-xylose blood concentration decrease after a certain time, modeled by a rate k_{elim} (min^{-1}). It is admitted that metabolization by the tissue and in the gut can be considered as negligible, making renal clearance the main factor of D-xylose elimination; therefore, a single rate of elimination from the plasma compartment is relevant. This model is mainly a discretized variant of the model of (Salinari et al., 2011).



(a) Reaction network

$$\begin{aligned}
\dot{X}_s(t) &= -k_{empt} \cdot X_s(t) \\
\dot{X}_{g1}(t) &= k_{empt} \cdot X_s(t) - (\alpha_1 \cdot k_{abs} + k_{trans}) \cdot X_{g1}(t) \\
&\vdots \\
\dot{X}_{gn}(t) &= k_{trans} \cdot X_{g_{n-1}}(t) - \alpha_n \cdot k_{abs} \cdot X_{gn}(t) \\
\dot{X}_p(t) &= Ra_X(t) - k_{elim} \cdot X_p(t) \\
Ra_X(t) &= k_{abs} \cdot (\sum_{i=1}^{n} \alpha_i \cdot X_{gi}(t)) \text{ and } \sum_{i=1}^{n} \alpha_i = 1
\end{aligned}$$

(b) ODE system

$$\begin{aligned}
\dot{X}_s(0) &= \frac{D_X}{BW \cdot V_{D_X}(BW)} \\
\dot{X}_{g1}(0) &= 0 \\
&\vdots \\
\dot{X}_{gn}(0) &= 0 \\
\dot{X}_p(0) &= 0
\end{aligned}$$

(c) Initial conditions

Figure 1: Multi-compartment model.

We also use a "jejunal injection" variant of the model, that is used to fit the *jejunal bolus dataset*. This variant is obtained by removing the variable X_s from the model and changing the initial value of X_{g1} to $\frac{D_X}{BW \cdot V_{D_X}(BW)}$, in order to model the injection of D-xylose directly into the intestine.

3.2 Parameter Estimation

Using our various available experimental datasets, we adopt a parameter estimation strategy that minimizes the risks of non-identifiability. For this, we estimate parameters using two datasets at the same time: the *oral bolus dataset* (on the main model) and the *jejunal bolus dataset* (on its jejunal variant). The estimated parameters are the rates k_{empt}, k_{abs} and k_{elim}, in addition to the absorption distribution parameters α_1, ..., α_n. All these parameters were considered common to both models, except for k_{empt} that does not exist in the jejunal variant.

Technically, we fit the mean values of the plasma D-xylose data X_p (purple bullets in Figure 2) taking into account the standard deviation (purple shaded area) to minimize the Negative Log-Likelihood Loss ($NLL-Loss$). This is achieved using the CMA-ES (Covariance matrix adaptation evolution strategy) numerical optimization algorithm (Hansen, 2023). All implementation steps (data pre-processing, model implementation and numerical analyses) were made in the *Julia* programming language (v1.8.2) with the following packages: CMAEvolutionStrategy (v0.2.6), DifferentialEquations (v7.7.0), DiffEqParamEstim (v2.0.1), ModelingToolkit (v8.46.1), Catalyst (v12.3.2), LikelihoodProfiler (v0.5.0) and Plots (v1.38.5).

Table 1: Parameter values estimated by fitting simultaneously the *oral* and *jejunal bolus datasets* with, respectively, the model and its jejunal variant (NLL-Loss: 44.035).

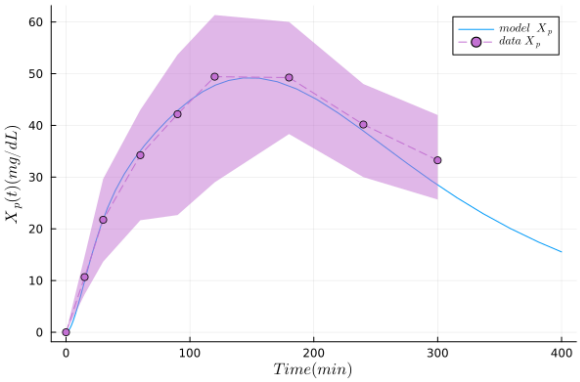
$\mathbf{k}_{empt}$ (min^{-1})	$\mathbf{k}_{abs}$ (min^{-1})	$\mathbf{k}_{elim}$ (min^{-1})
0.0379	0.222	0.00628

The parameter values that are obtained for k_{empt}, k_{abs} and k_{elim} are reported in Table 1. As can be seen on Figure 2, the model performs a good fitting of both the oral and jejunal datasets.

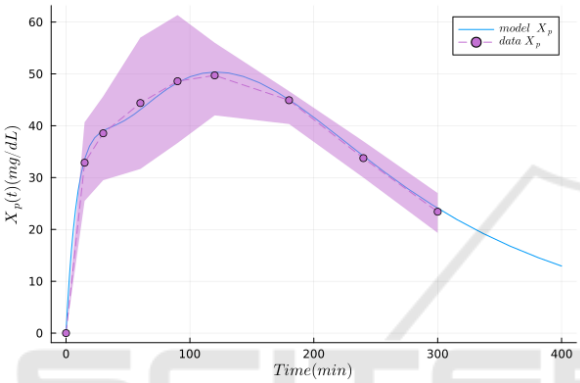
3.3 Practical Identifiability Analysis

Parameter estimation allows to find *one* set of parameter values that makes a model fit the data, but does not guarantee that there aren't any other values that could *equally* or *satisfyingly* fit the data. Indeed, experimental data are noisy and part of the fitting deviation is to be attributed to experimental error. Intuitively, assuming acceptable error intervals for the observed variables, if there is a "unique" set of parameter values that makes the observed variables fit the data within these intervals, then the model is said *practically* identifiable.

Identifiability analysis is an important step in assessing the quality of a model. In this paper, we consider practical identifiability based on the profile likelihood method (Raue et al., 2009). This method investigates the practical identifiability *locally*, that is, near



(a) Results of the model fitting the *oral bolus dataset*



(b) Results of the jejunal variant of the model fitting the *jejunal bolus dataset*

Figure 2: Results of the main model and its jejunal variant, respectively fitting the *oral* and *jejunal bolus datasets* featuring plasma D-xylose (NLL-Loss: 44.035). The dots and the dashed lines represent the mean experimental values, the envelope is the standard deviation, and the plain lines are the simulations produced with the model.

Table 2: Practical identifiability analysis results. Here, each value represents a confidence interval bound (denoted as *C.I.*) that is reached, meaning complete practical identifiability for the model. Missing values would have denoted unreached bounds and thus incomplete identifiability.

	C.I. lower bound	**C.I upper bound**
k_{empt}	0.0374	0.0920
k_{abs}	0.222	0.328
k_{elim}	0.00622	0.00708

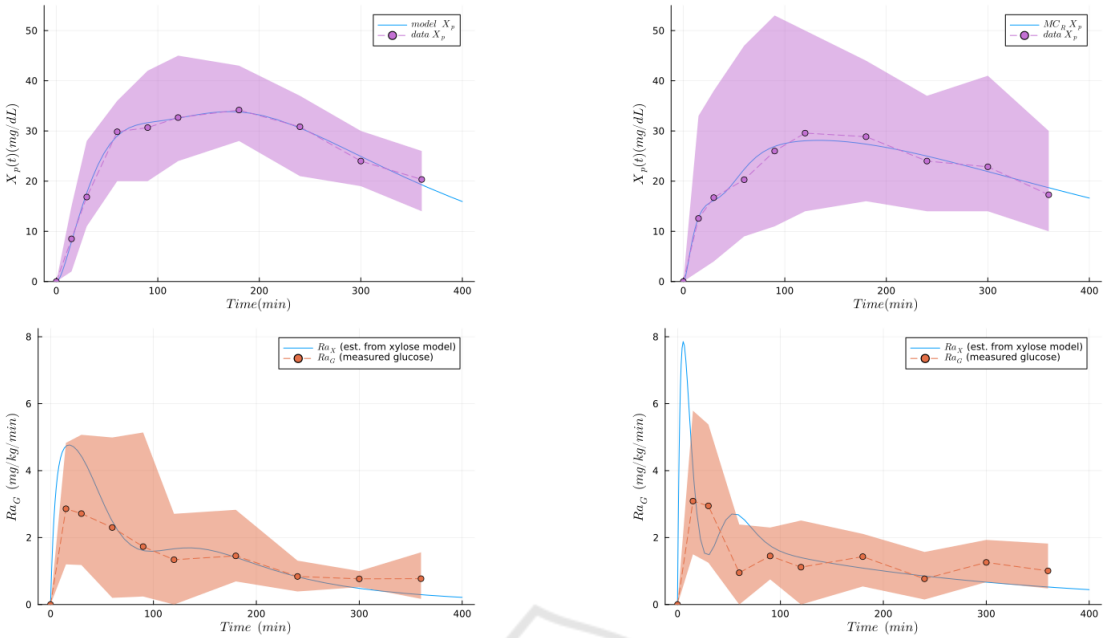
the estimated value of a given parameter. For this, we used the Julia package LikelihoodProfiler (v0.5.0). This tool locally analyses each parameter in a given interval to scan, which gives a confidence interval bound if the parameter is identifiable, or none if the tool has reached the given scan interval bounds or if no identifiability gain is detected along this interval. As it is an exploratory step, we gave a relatively large interval to scan for each parameter of interest. We set the confidence interval to 95%.

The confidence intervals found for each parameter are collected in Table 2. We actually ignore the identifiability of the speed of intestinal transit and the distribution of absorption parameters that are irrelevant for the present work and, hence, set as constants for this identifiability analysis. These intervals indicate total identifiability for the three relevant parameters: k_{empt}, k_{abs} and k_{elim}. The results can be interpreted as an indication of the good relevance of the collected datasets and especially the good reliability of the estimation of our main parameter of interest, k_{abs}. This analysis has been performed in the same setting that was used for fitting in Section 3.2, that is, on the main model and its jejunal variant simultaneously.

3.4 Prediction of The Rate of Glucose Absorption from The Dataset of Intestinal Resection

In order to validate the usefulness of our model, we test its capability to predict the *rate of appearance of exogenous glucose* (Ra_G) both in normal condition and after an intestinal resection. Recall that this rate corresponds to the part of the concentration of glucose per unit of time appearing in blood that is originating from the meal. This rate was experimentally monitored using the dual tracer protocol. We show in the following that the model is able to adapt to data obtained after intestinal resection, which is considered to experimentally simulate a change in the mechanisms of glucose absorption. In this study, since the setting and individuals are different from the datasets used above, we re-evaluate all parameters (rates and absorption parameters) except the elimination (considered untouched by the operation) before and after intestinal resection. However, since our model is designed for D-xylose, we do not directly train it on the available glucose data: instead, we train it on the available D-xylose datasets (not featuring double-tracer data, but only D-xylose concentration in blood over time) and compare the results with the glucose dynamics form the glucose datasets.

Finally, we compare the rate of D-xylose appearance (Ra_X) computed using the model (with the formula given in Figure 1b) and compare it with the Ra_G experimental data (the rate of appearance of exogenous *glucose*) obtained with the double-tracer method. This result is presented in Figure 3. As we can see, although the values of the parameters were estimated on *D-xylose* plasma measurments, the model gives a relatively satisfying prediction of the rate of appearance of exogenous *glucose* (Figure 3, lower plots). This tends to indicate that D-xylose



(a) Results of the model fitting the *oral bolus before intestinal resection dataset*.

(b) Results of the model fitting the *oral bolus after intestinal resection dataset*.

Figure 3: Comparing the rate of glucose exogenous appearance (Ra_G) from double tracer experiment, the gold standard method, to the generated rate of appearance of D-xylose (Ra_X), obtained from parameter estimation (NLL-Loss: 52.459) on the same population. The dots and the dashed lines represent the mean experimental values, the envelope is the standard deviation, and the plain lines are the simulations produced with the model. The top figures represent the plasma D-xylose (used for fitting the parameters). The bottom figures represent the simulated rate of absorption of D-xylose (Ra_X) from the model, and the observed rate of absorption of glucose (Ra_G) from double-tracer experiments. In both experimental conditions (pre- and post-resection) we can observe a relatively good fitting between the glucose and the D-xylose, despite the absence of a glucose model in this work.

might be an acceptable marker for glucose absorption. Note that the difference of the rates of appearance between glucose and D-xylose after a resection might reflect, on the one hand, that Ra_x is the exclusive reflection of the gastric emptying and the intestinal absorption, whereas on the other hand, Ra_G reflects these two mechanisms in addition to the inevitable hepatic glucose metabolization, despite the use of the gold standard method.

4 RELATIVE ROLES OF GASTRIC EMPTYING AND INTESTINAL ABSORPTION

In this section, we propose to compare the relative roles that gastric emptying and intestinal absorption play in the appearance of D-xylose in the blood, according to our model. For this, we first perform a global sensitivity analysis, which is designed to assess the impact of the model parameters on a chosen model output. In our case, such analysis would assess which parameter is the most impactful on the D-xylose appearance, especially between gastric emptying and intestinal absorption. Since we considered D-xylose as a relevant biomarker for glucose exogenous appearance, it is expected that the model is more sensitive to intestinal absorption than gastric emptying. In addition to the sensitivity analysis, we estimated the parameters on a model inspired by Dalla Man and colleagues (Dalla Man et al., 2006) characterized by a detailed gastric emptying modeling and a simplified intestinal modeling.

4.1 Global Sensitivity Analysis

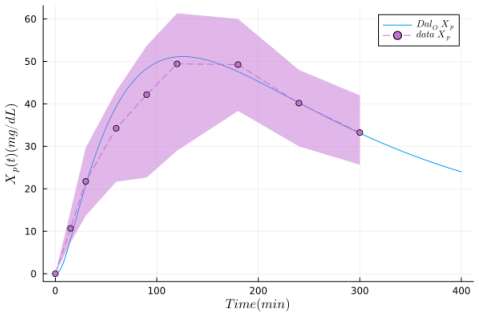
The rate of exogenous sugar appearance (either Ra_X for D-xylose or Ra_G for glucose) depends not only on the rate of intestinal absorption but also on the rate of gastric emptying. Hence, both gastric emptying and intestinal absorption events are potentially contributing to IGA. As we seek for a model that can assess the intestinal activity to profile any individual, it is important to check which factor is the most impactful on IGA.

Global sensitivity analysis allows to understand how the uncertainty or variability in the inputs of a model affects the output or outcome of the model. It helps to identify which parameters have the most significant impact on the model's results. In this work, the sensitivity analysis has been done on the model (without the jejunal variant) using Sobol indices (Soboĺ, 1993). For the model's output, we consider the area under the curve of D-xylose's rate of appearance at 180 minutes, noted AUC_{Ra_X}. It corresponds to the integration of Ra_X, that is, to the total quantity of D-xylose that has reached the blood at a given time t independently from the influence of the rate of elimination k_{elim}. In the absence of tracer methods (as it is the case for D-xylose in this work), computing AUC_{Ra_X} is of interest to assess D-xylose absorption because observing only its concentration in plasma (X_p) would be also influenced by the elimination rate. Furthermore, by checking the output at the maximum time monitored (180 min), we wanted to ensure that the gastric emptying has way less influence on the rate of appearance than the intestinal absorption, hence making sure that D-xylose can potentially be used as a biomarker to assess Ra_X (and eventually Ra_G).

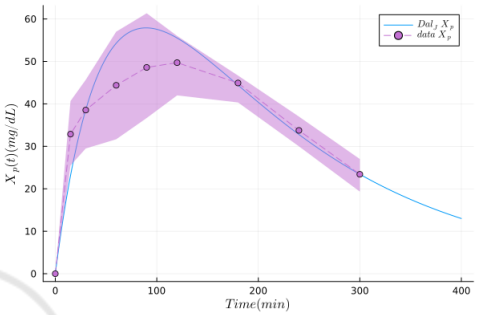
We use the Julia package GlobalSensitivity (v2.1.4) to perform this analysis for AUC_{Ra_X}. This analysis systematically states the importance of intestinal absorption, without denying the role of gastric emptying, for both parameters. Indeed, it indicates a first order Sobol index of 0.05 for k_{empt} and a first order Sobol index index of 0.95 for k_{abs}.

4.2 Model with Complex Gastric Emptying

To validate furthermore the degree of implication of intestinal absorption over gastric emptying on the glucose or D-xylose appearance in the blood, we compared our results with another model featuring a more complex gastric emptying part, inspired from the works of Dalla Man and colleagues (Dalla Man et al., 2006). This model features two compartments for the stomach contents, the first (X_{s_1}) representing non-grinded food and the second (X_{s_2}) representeing grinded food (as opposed to only one compartment for the model of Figure 1) but only one compartment (X_g) for the intestine (as opposed to several compartments for the model of Figure 1). Moreover, the rate of gastric emptying k_{empt} from X_{s_2} to X_g is not a constant value but depends on the sum of the two variables that represent the total content of the stomach ($X_{s_1} + X_{s_2}$), on the initial bolus (D_X) and on other constant parameters (k_{min}, k_{max}, a and b). Intuitively,



(a) X_p from oral bolus.



(b) X_p from jejunal bolus.

Figure 4: Results of parameter estimations of the model inspired from Dalla Man et al. on the *oral* and *jejunal bolus datasets* (NLL-Loss: 47.416). The dots and the dashed lines represent the mean experimental values, the envelope is the standard deviation, and the plain lines are the simulations produced with the model of Section 4.2.

this rate is U-shaped and reaches its maximum value (k_{max}) at the beginning and the end of the griniding (when the stomach is almost full or almost empty) and reaches its minimum value (k_{min}) in-between.

The values of all constant parameters were obtained with the same data (*oral bolus dataset* and *jejunal bolus dataset*) and the same fitting method than the model of Section 3. As a reminder, the experimental dataset features the D-xylose concentration over time, measured in the peripheral blood, both after an oral bolus and after a bolus directly injected in the jejunum, and the fitting of the parameters is performed using both experimental conditions at once. The idea is to check if a model with a more complex stomach and gastric emptying coupled with a simpler intestine modeled as a single compartment is able to fit this dataset as efficiently as the model of Figure 1. The result of this experiment is given in the simulation of Figure 4, showing that the more complex gastric part of the model is not able to fit the data as well as the model of Figure 1. Hence, combined with the sensitivity analysis on the multi-compartment model, we demonstrate the necessity to use the model of Figure 1 to reflect D-xylose appearance.

5 CONCLUSIONS AND PERSPECTIVES

In this work, we propose a multi-compartment model of postprandial D-xylose dynamics as a first step towards a predictive model of intestinal glucose absorption. This model is based on three major parameters representing the (linear) rates of gastric emptying, intestinal absorption and elimination, and models the intestine as a succession of compartments, thus introducing a delay that models the intestinal transit. We calibrated the model using a tailored dataset from several minipig populations that underwent oral, intravenous or jejunal administration of D-xylose, as well as intestinal resection. We studied the identifiability and the sensitivity of its parameters.

This model presents good performances in terms of goodness-of-fit, even with the data of jejunal injection, especially when compared with another model where the gastric part is more complex but the intestinal part is simplified, and which does not fit the data of jejunal injection data as well. This suggests that the chosen multi-compartment modeling of the intestine is relevant, and emphasizes the important role of intestinal absorption. Furthermore, the model appeared to be identifiable for all relevant parameters.

Finally, we also compared the rate of appearance of D-xylose predicted by the model with the actual rate of appearance of exogenous glucose (Ra_G), that is, glucose only coming from the meal and not from kidney storage, for instance. These results are very interesting as they corroborate that D-xylose could be a valuable marker of intestinal absorption. It reinforces the fact that our model is a good candidate to predict Ra_G, at least qualitatively.

Besides of experimental investigations, further work is necessary to improve, or better take advantage of, the ability of the model to predict Ra_G. Also, we plan to propose a simplified model of the glucose-insulin regulation system based on the minimal-model of (Bergman et al., 1979) with an accurate D-xylose-based model of IGA. Finally, datasets on humans that underwent glucose and D-xylose bolus administrations could help translate this model to humans. In the long term, it is hoped that this model could be applied to humans and could help in a medical setting to diagnose patients with abnormal intestinal glucose absorption.

ACKNOWLEDGMENTS

This work was supported by project *MIGAD* (ANR-21-CE45-0017) of the French National Research Agency (ANR).

REFERENCES

Baud, G., Raverdy, V., Bonner, C., Daoudi, M., Caiazzo, R., and Pattou, F. (2016). Sodium glucose transport modulation in type 2 diabetes and gastric bypass surgery. *Surgery for Obesity and Related Diseases*, 12(6):1206–1212. Diabetes Special Issue.

Bergman, M. et al. (2018). Lessons learned from the 1-hour post-load glucose level during ogtt: Current screening recommendations for dysglycaemia should be revised. *Diabetes/metabolism research and reviews*, 34(5):e2992.

Bergman, R. N., Ider, Y. Z., Bowden, C. R., and Cobelli, C. (1979). Quantitative estimation of insulin sensitivity. *American Journal of Physiology-Endocrinology and Metabolism*, 236(6):E667.

Dalla Man, C., Camilleri, M., and Cobelli, C. (2006). A system model of oral glucose absorption: Validation on gold standard data. *IEEE Transactions on Biomedical Engineering*, 53(12):2472–2478.

Elashoff, J. D., Reedy, T. J., and Meyer, J. H. (1982). Analysis of gastric emptying data. *Gastroenterology*, 83(6):1306–1312.

Fujita, Y., Kojima, H., Hidaka, H., Fujimiya, M., Kashiwagi, A., and Kikkawa, R. (1998). Increased intestinal glucose absorption and postprandial hyperglycaemia at the early step of glucose intolerance in otsuka long-evans tokushima fatty rats. *Diabetologia*, 41:1459–1466.

Goutchtat, R., Marciniak, C., Caiazzo, R., Verkindt, H., Quenon, A., Rabier, T., Lapiere, S., Raverdy, V., Hubert, T., and Pattou, F. (2022). 1361-p: D-xylose test as a biomarker for glucose intestinal absorption in humans and minipigs. *Diabetes*, 71(Supplement_1).

Hansen, N. (2023). The cma evolution strategy: A tutorial.

Raue, A., Kreutz, C., Maiwald, T., Bachmann, J., Schilling, M., Klingmüller, U., and Timmer, J. (2009). Structural and practical identifiability analysis of partially observed dynamical models by exploiting the profile likelihood. *Bioinformatics*, 25(15):1923–1929.

Salinari, S., Bertuzzi, A., and Mingrone, G. (2011). Intestinal transit of a glucose bolus and incretin kinetics: a mathematical model with application to the oral glucose tolerance test. *American Journal of Physiology-Endocrinology and Metabolism*, 300(6):E955–E965.

Soboĺ, I. (1993). Sensitivity estimates for nonlinear mathematical models. *Math. Model. Comput. Exp.*, 1:407.

Toffolo, G., Basu, R., Dalla Man, C., Rizza, R., and Cobelli, C. (2006). Assessment of postprandial glucose metabolism: conventional dual-vs. triple-tracer method. *American Journal of Physiology-Endocrinology And Metabolism*, 291(4):E800–E806.

Tricò, D., Mengozzi, A., Frascerra, S., Scozzaro, M. T., Mari, A., and Natali, A. (2019). Intestinal glucose absorption is a key determinant of 1-hour post-load plasma glucose levels in nondiabetic subjects. *The Journal of Clinical Endocrinology & Metabolism*, 104(6):2131–2139.