



HAL
open science

Modeling Intestinal Glucose Absorption from D-xylose Data

Danilo Dursoniah, Maxime Folschette, Rebecca Goutchtat, Violeta Raverdy,
François Pattou, Cédric Lhoussaine

► **To cite this version:**

Danilo Dursoniah, Maxime Folschette, Rebecca Goutchtat, Violeta Raverdy, François Pattou, et al.. Modeling Intestinal Glucose Absorption from D-xylose Data. 15th International Conference on Bioinformatics, Models, Methods and Algorithms, Feb 2024, Rome, Italy. hal-04329210v1

HAL Id: hal-04329210

<https://hal.science/hal-04329210v1>

Submitted on 7 Dec 2023 (v1), last revised 22 Apr 2024 (v3)

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Modeling Intestinal Glucose Absorption from D-xylose Data

Danilo Dursoniah¹^a, Maxime Folschette¹^b, Rebecca Goutchtat², Violeta Raverdy², François Pattou² and Cédric Lhoussaine¹^c

¹Univ. Lille, CNRS, Centrale Lille, UMR 9189 CRISTAL, F-59000 Lille, France

²Univ. 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, for the first time, a model-based assessment of IGA based on D-xylose dynamics in blood after oral absorption. We show that a multi-compartment model of intestinal absorption can fit very well D-xylose data obtained from different experimental conditions and be a good qualitative estimate of IGA. And addition, 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 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 (Dalla Man et al., 2007) 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, measuring this rate experimentally is a difficult challenge. Indeed, it cannot be deduced from other easily observable variables like the concentration of glucose in blood, because other mechanisms occur all the time: glucose excretion (by the kidneys), glucose production (by the liver) and metabolization (by the tissues), regulated by insulin, as illustrated in Figure 1a.

^a <https://orcid.org/0009-0007-6159-1966>

^b <https://orcid.org/0000-0002-3727-2320>

^c <https://orcid.org/0000-0002-3970-3761>

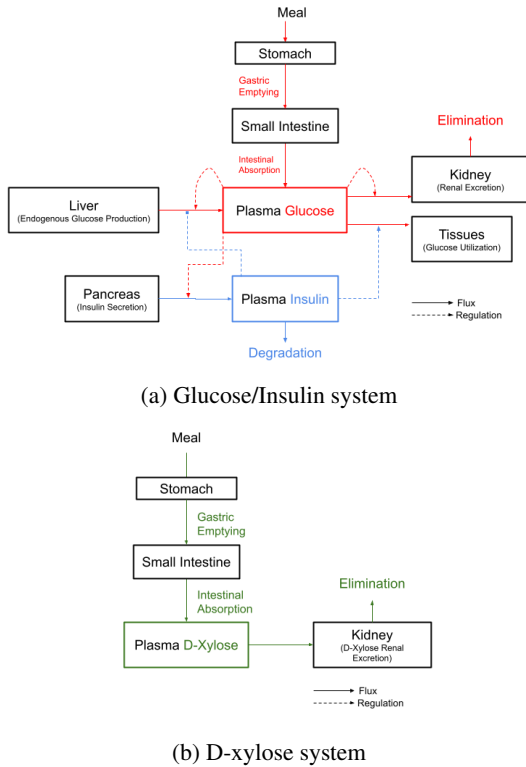


Figure 1: Simplified diagrams of the regulated glucose/insulin system and the unregulated D-xylose system.

In addition, the direct measurement of Ra_G requires an access to the portal vein, which is generally hardly feasible and impossible on humans. The current approach to experimentally measure Ra_G is to perform oral glucose tests with multiple isotopic tracers (dual- or triple-tracer) that consist in injecting 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. As illustrated in Figure 1b, 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 metabolism 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 of simpler 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.

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. While being simple, we show that our model can fit time series of D-xylose data obtained in different experimental conditions with a good accuracy and, most importantly, that it can predict Ra_G validated with tracer data. In addition, to decipher the relative contribution of gastric emptying and intestinal absorption to D-xylose dynamics, we show that an alternative model based on a complex two-compartment model of gastric emptying and simple exponential intestinal absorption cannot fit equally well the experimental data. Finally, based on our model, we study a possible marker of glucose absorption independently of gastric emptying.

Outline Section 2 presents the experimental datasets. Section 3 presents the model of D-xylose dynamics, the results of parameter identification, and the fitting of the model with the glucose rate of absorption obtained by double tracer. In Section 4, we present the results of parameter identifiability and sensitivity. In Section 5, we discuss the results and present some future work.

2 Minipigs Datasets for Parameters Estimations

For the model calibration, we use experimental data, provided by our clinical research partner (Goutchtat et al., 2022), that involves Göttingen minipig datasets. This species is indeed well adapted for gastrointestinal experiments and has a physiology that is close to the human one, thus allowing experiments that were not ethically possible on humans. For our problematic, different experiments have been performed to monitor sugar in the blood after an intake of a bolus of sugar using intravenous, intestinal or oral administration. This entails several subpopulations of pigs.

- *Intravenous bolus subpopulation*: in this cohort, the experiment consists of administrating a single shot of solution of sugar in the blood, including 30 g of D-xylose. These data allow to estimate

the volume of distribution V_D that is used to convert both the initial amount of sugar into a concentration and the rate of exogenous appearance into the right dimension (see below).

- *Intestinal (or jejunal) bolus subpopulation*: in this group, the stomach is bypassed and the meal is directly administrated in the small intestine, and more precisely in its proximal half, the jejunum. The blended meal includes 30 g of D-xylose. This experiment is interesting to study gastric emptying, as the same subpopulation of minipigs that underwent this experiment also got an oral administration in a normal state (before experimental surgery). From a modeling point of view, it consolidates the estimated rate k_{empt} of gastric emptying (part of the bolus transferred from the stomach to the intestine).
- *Oral bolus subpopulation after intestinal resection*: in this case, about 80% of the mid-part of the small intestine has been removed, before the oral administration of the meal (containing 30 g of D-xylose). This experiment 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 benefits 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).
- All these subpopulations also underwent, before their respective experimental bolus or surgery, an oral administration of a meal to monitor blood sugar in the normal state.

As stated above, we need to assess the volume of distribution of D-xylose V_{D_X} . This volume of distribution is the total volume of fluid (mainly blood, but also interstitial fluids) that D-xylose can occupy once absorbed by the intestine: it serves as a reference to compute the concentration of D-xylose in the body. 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 the following equation:

$$V_{D_X} = \frac{D_X}{BW \cdot X_p}$$

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). To obtain this value, we perform a simple model fitting from observations of

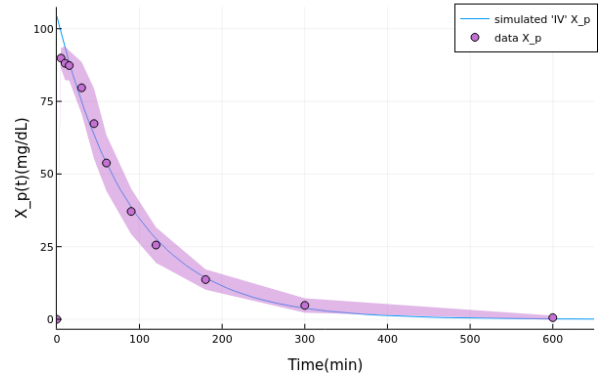


Figure 2: Results of the simple intravenous model fitting the intravenous injection dataset in order to estimate the volume of distribution V_{D_X} . The estimated parameter is $k_{elim} = 0.00960$ with a log-likelihood loss of 29.49956. The bullets represent the mean values of the dataset, the envelope represents its standard deviation, and the line represents the model simulation.

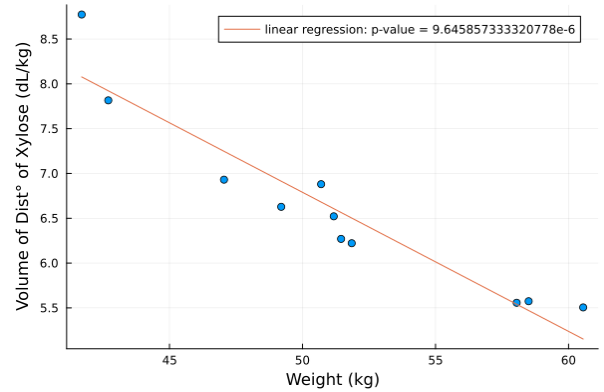


Figure 3: Tracing the significant linear correlation between the body weight of each individual that underwent intravenous injection and their respective volume of distribution. Pearson coefficient: -0.94725 .

D-xylose dynamics after an intravenous injection, reported in Figure 2, which features the curves of the observed and simulated D-xylose in plasma, X_p , over time. Given that, in true experimental conditions, the intravenous injection procedure spreads over 5 min while the elimination starts immediately, the value we actually consider for X_p is the concentration obtained for the curve extrapolated to 0. From this work, we found a significant linear correlation between the body weight and the volume of distribution as shown in Figure 3. 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 undergo an intravenous injection experiment.

All these datasets were used to calibrate the models presented in the next section.

3 Model

This section presents the main model of this work and results provided by this model.

3.1 Multi-Compartment model

The model is given in Figure 4 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:

- one variable X_s modeling the stomach,
- one variable X_p modeling plasma,
- n variables X_{g1}, \dots, X_{gn} modeling the intestinal tract, where $n = 10$ for all following numerical analyses.

The rate k_{empt} (min^{-1}) models gastric emptying, that is, the 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 4.3.

Intestinal transit is modeled as a flux of D-xylose between the compartments X_{g1}, \dots, X_{gn} modeling the intestine. More precisely, this flux allows D-xylose to transit from each compartment, X_{gi} , to the next, X_{gi+1} . We assume that this flux is uniform with rate k_{trans} (min^{-1}) defined by the following equations:

$$k_{trans} = \frac{1}{\tau} \quad \tau = \frac{L}{u \cdot n}$$

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 *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_{gi} , the rate of absorption is modulated by a strictly positive parameter α_i . The sum of all parameters $\alpha_1, \dots, \alpha_n$ 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 therefore don't force any particular distribution, and the parameters α_i are estimated.

Finally, here, "elimination" is a generic term to designate both D-xylose renal clearance and metabolism, both resulting in D-xylose blood concentration decrease after a certain time, modeled by a rate k_{elim} (min^{-1}). It is admitted that metabolism 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.

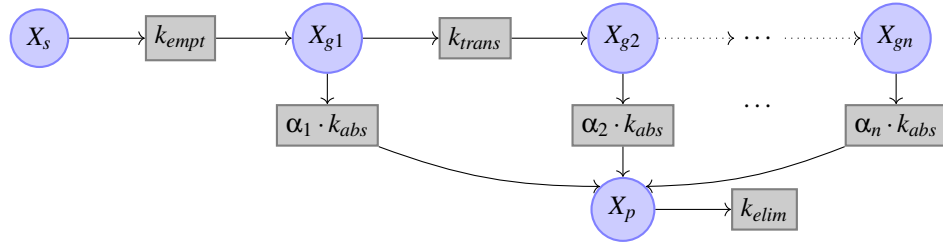
This model is a discretized variant of the model of (Salinari et al., 2011), which models the intestine as a long continuous compartment inside which the meal bolus moves with a certain speed; the rate of absorption thus depends on the position of the bolus inside this unique compartment. In the present work, this is instead modeled as a series of successive compartments with different absorption factors ($\alpha_1, \dots, \alpha_n$). The point is to take into account both the transport of D-xylose along the intestinal tract, and the non-uniform distribution of glucose transporters (proteins involved in the absorption of glucose from the gut to the blood) along the intestinal tract.

We also use a "jejunal injection" variant of the model, that is used to fit the data of the individuals that underwent jejunal injection. 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 dataset (on the main model) and the jejunal 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 $\alpha_1, \dots, \alpha_n$. 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 5) taking into account the standard deviation (purple shaded area) to minimize the Negative Log-Likelihood 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), Differ-



(a) Reaction network

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

(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 4: Multi-compartment model.

k_{empt} (min^{-1})	k_{abs} (min^{-1})	k_{elim} (min^{-1})
0.0379	0.2223	0.007

Table 1: Parameter values estimated by fitting simultaneously the oral and jejunal datasets with, respectively, the model and its jejunal variant. Obtained loss: 44.035.

entialEquations (v7.7.0), DiffEqParamEstim (v2.0.1), ModelingToolkit (v8.46.1), Catalyst (v12.3.2), LikelihoodProfiler (v0.5.0) and Plots (v1.38.5).

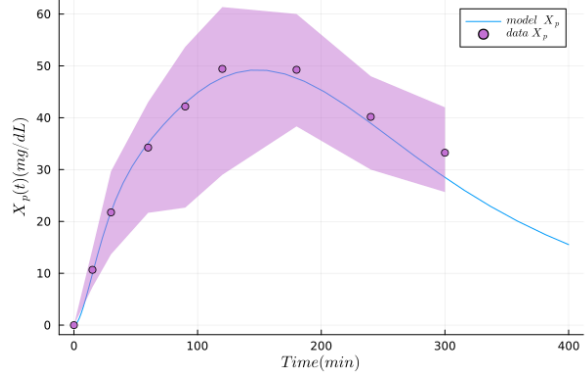
The parameter values that are obtained for k_{empt} , k_{abs} and k_{elim} are reported in Table 1. As can be seen on Figure 5, the model performs a good fitting of both the oral and jejunal datasets.

3.3 Prediction of the rate of glucose absorption from dataset of intestinal resection

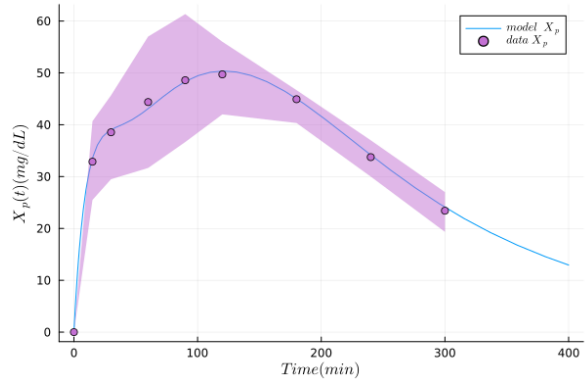
[TODO: Commentaire de Rebecca ci-dessous; j'ai essayé d'y répondre dans le paragraphe suivant. Pourquoi avoir fait ça dans un contexte de résection intestinale et non dans un contexte classique ? Qu'est-ce que la résection vous apporte ? Est-ce que ce ne va pas être confusant ?

Je trouve que votre objectif est peu clair en effet. Ici vous voulez montrer que le modèle de Ra D-Xylose est proche du modèle de RaE Glucose ?

Côté clinique, cela nous intéresse de le faire car cela soutient le fait qu'on peut substituer la méthode



(a) Results of the model fitting the oral dataset



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

Figure 5: Results of the main model and its jejunal variant, respectively fitting the oral and jejunal plasma D-xylose datasets.

double traceur par la méthode D-Xylose. De votre côté, est-ce que ça vous permet réellement de valider le modèle computationnel ? Car vous voulez prédire des données obtenues par substrat 1 + modèle 1 avec des données obtenues par substrat 2 + modèle 2...]

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) expect 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 datasets: 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 from the glucose datasets.

Finally, we compare the rate of D-xylose appearance (Ra_X) computed using the model (with the formula given in Figure 4b) 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 6. As we can see, although the values of the parameters were estimated on *D-xylose* plasma measurements, the model gives a relatively satisfying prediction of the rate of appearance of exogenous *glucose* (Figure 6, lower plots). **This tends to indicate that D-xylose might be an acceptable marker for glucose absorption.**

4 Model analyses

In this section, we propose as post-model-fitting assessment: a practical identifiability analysis based on the profile likelihood method and a global sensitivity analysis. On the one hand, the profile likelihood assesses the relevance of the estimated parameters values by the model, beyond the goodness-of-fit on the dataset. Indeed, it is possible that several parameters values are allowed by the model. On the other hand, the global sensitivity analysis is designed to assess the

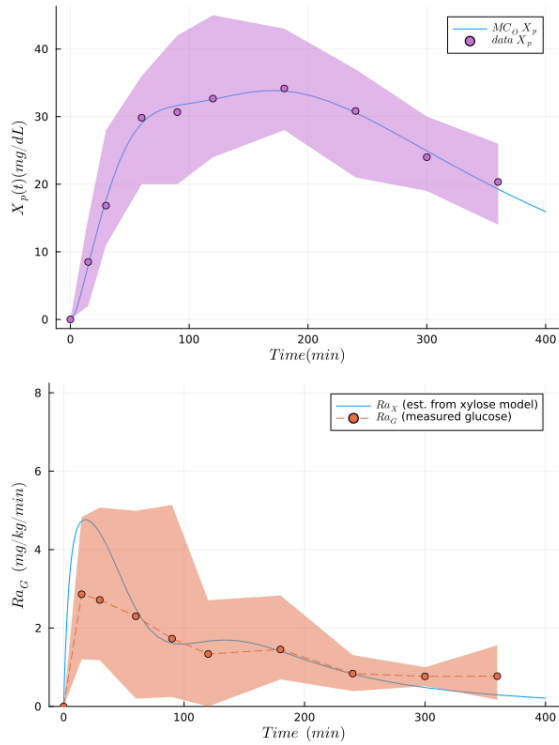
impact of the model parameters on a chosen model output. In our case, such analysis would assess which parameter is the most impactful on the D-xylose appearance, especially between gastric emptying and intestinal absorption. Since is considered D-xylose a relevant biomarker for glucose exogenous appearance, it is expected that the model is more sensitive to intestinal absorption than gastric emptying. In addition to the profile likelihood and 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 Practical identifiability analysis

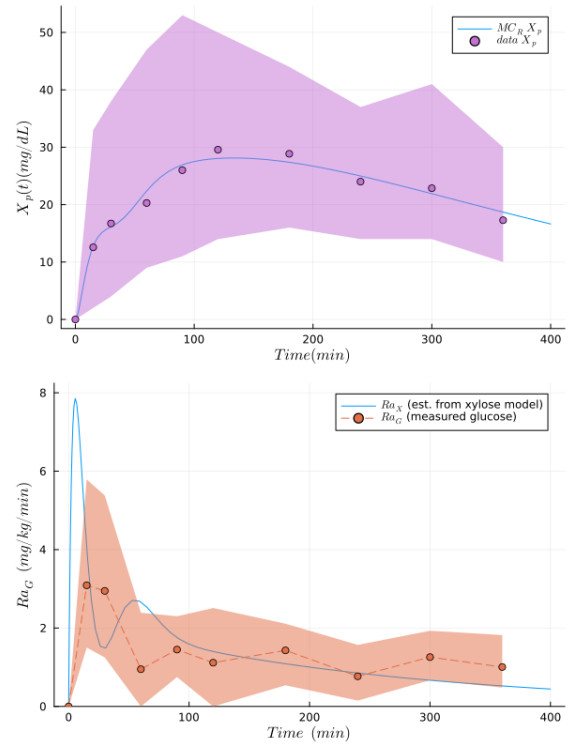
Parameter	Confidence interval	Confidence interval
	lower bound	upper bound
k_{empt}	0.00781	unreachable
k_{abs}	0.02796	unreachable

Table 2: Practical identifiability analysis table on the gastric emptying rate k_{empt} and the intestinal absorption rate k_{abs} for the model. Reaching both confidence interval bounds would mean complete practical identifiability for the parameter, and no bounds reached would indicate non-identifiability. Here, only one of the two bounds is reached for each parameter, meaning partial identifiability.

Parameter estimation allows to find *one* set of parameter values that makes a model fit the data. It 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. However, if non-identifiability can be attributed to the data (e.g., because of limited amount or too noisy data), it can also be attributed to the model itself in which changing the values of some parameters can always be compensated by other parameter values whatever the data. In the latter case, we say that the model is *structurally* non-identifiable (Bellman and Åström, 1970). 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 the estimated value of a given parameter. For this, we used the Julia package LikelihoodProfiler (v0.5.0). This tool locally



(a) Results of the model fitting oral datasets, pre-resection.



(b) Results of the model fitting oral datasets, post-resection.

Figure 6: 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 on the same population. The dots represent the mean experimental values, the envelope is the standard deviation, and the 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 direct relatively good fitting between the glucose and the D-xylose, despite the absence of glucose model in this work.

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, hence, set as constants. These intervals indicate total identifiability for k_{elim} whereas partial identifiability is found for k_{empty} and k_{abs} . The results can be interpreted as an indication of the good relevance of the collected datasets and the relatively good reliability of the estimation of our main parameter of interest k_{abs} . This analysis has been performed on the oral model.

4.2 Global sensitivity analysis

[TODO: Commentaire de Rebecca, non traité pour le moment : Je pense que pour quelqu'un qui ne connaît pas le sujet, la nuance n'est pas claire.

Essayer peut-être de dire un truc du genre : IGA, et par conséquent l'apparition du glucose/D-Xylose systémique dépendent à la fois de la vidange gastrique et de facteurs propres à l'intestin (transporteurs du glucose par exemple). L'idée ici de voir s'il est possible de déterminer si de potentielles variations de l'IGA proviennent de variations de la vitesse de la vidange gastrique ou bien de variations propres à l'intestin (nombre et/ou efficacité des transporteurs du glucose).

Pour moi, il s'agit plus d'un exemple pour illustrer l'intérêt de votre modèle que d'une étape de sa validation. Peut-être serait-il utile de le préciser ?]

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. Indeed, if several factors, such as the number of sugar transporters in the intestine cells, have a direct influence on intestinal absorption, this absorption is still dependent on the quantity of sugar that the stomach delivers to the intestine. 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 is another process used to understand how the uncertainty or variability in the inputs of a mathematical or computational model affects the output or outcome of the model. It helps identify which input factors or variables have the most significant impact on the model's results. In other words, its goal is to figure out which factors matter the most and how they contribute to the overall variability of the model's predictions or outputs. Sobol indices are widely used measures in global sensitivity analysis. They quantify the contribution of each input factor or variable to the overall variability of a model's output. Sobol indices are calculated by decomposing the total variance of the model output into different components attributed to individual input factors or combinations of factors. They provide insights into the relative importance and interactions of different input variables in influencing the model's output (Sobol, 1993). In this work, the sensitivity analysis has been done on the model without the jejunal variant. For the model's output we separately consider the mean of D-xylose, X_p , and the area under the curve of its rate of appearance, noted AUC_{RaX} . AUC_{RaX} , 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_{RaX} is of interest to assess D-xylose absorption because simply observing its concentration in plasma (X_p) would be also influenced by the elimination rate.

We use the Julia package GlobalSensitivity (v2.1.4) to perform this analysis and obtain Figures 7 for X_p , and Figure 8 for AUC_{RaX} . This analysis systematically states the importance of intestinal absorption, without denying the role of gastric emptying, for both variables.

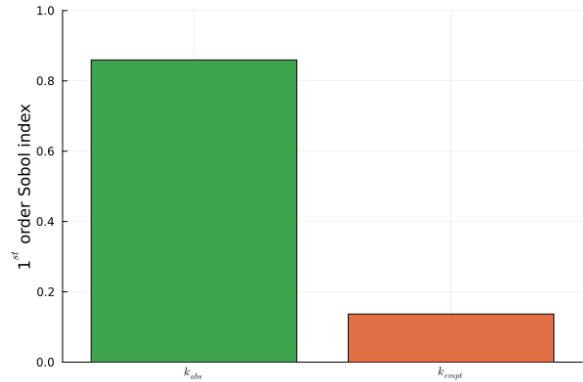


Figure 7: Results of the global sensitivity analysis of the mean of X_p over time.

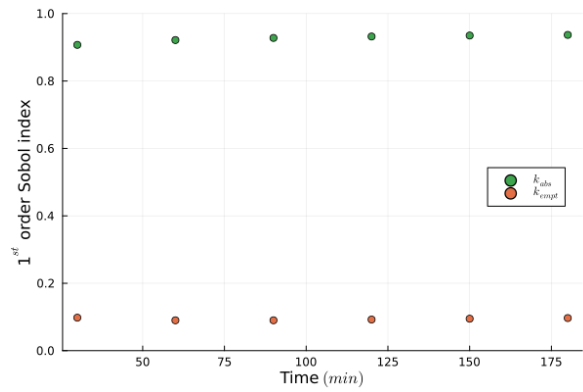


Figure 8: Results of the global sensitivity analysis of AUC_{RaX} over time.

4.3 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 is given in Figure 9 and features two compartments for the stomach contents, the first (X_{s1}) representing non-grinded food and the second (X_{s2}) representing grinded food (as opposed to only one compartment for the model of Figure 4) but only one compartment (X_g) for the intestine (as opposed to several compartments for the model of Figure 4). Moreover, the rate of gastric emptying k_{empt} from X_{s2} 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: $X_{s1} + X_{s2}$, on the initial bolus (D_X) and on other constant parameters (k_{min} , k_{max} , a and b). Intuitively, this rate is U-shaped and reaches its maximum value (k_{max}) at the beginning and the end of the grind-

ing (when the stomach is almost full or almost empty) and reaches its minimum value (k_{min}) in-between.

The values of all constant parameters in the model of Figure 9 were obtained with the same data 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 4. The result of this experiment is given in the simulation of Figure 10, showing that the more complex gastric part of the model is not able to fit the data as well as the model of Figure 4. Hence, combined with the sensitivity analysis on the multi-compartment model, we demonstrate the necessity to use the model of Figure 4 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. On the downside, the rates of gastric emptying and of intestinal absorption of our model are only partially identifiable.

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.

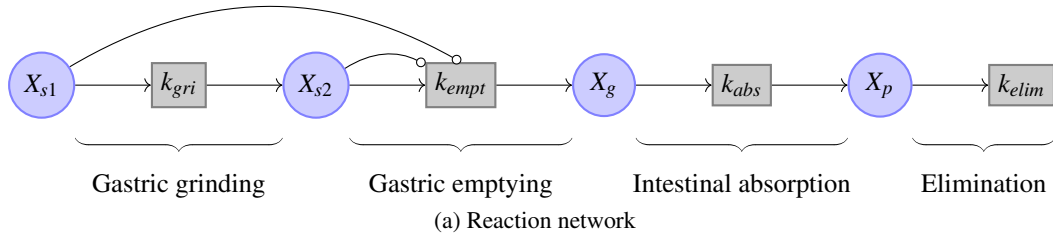
Besides of experimental investigations, further work is necessary to improve, or better take advantage of, the ability of the model to predict Ra_G . In particular, we need to understand to reasons for the partial identifiability of the parameters which could be addressed with a finer analysis of the profile likelihood and new experimental plans. 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. **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.**

5.1 Acknowledgments

This work was supported by a grant overseen by the French National Research Agency (ANR), for the project *MIGAD* (ANR-21-CE45-0017).

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.
- Bellman, R. and Åström, K. (1970). On structural identifiability. *Mathematical Biosciences*, 7(3):329–339.
- Bergman, M., Jagannathan, R., Buysschaert, M., Pareek, M., Olsen, M. H., Nilsson, P. M., Medina, J. L., Roth, J., Chetrit, A., Groop, L., 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.
- Dalla Man, C., Rizza, R. A., and Cobelli, C. (2007). Meal simulation model of the glucose-insulin system. *IEEE Transactions on biomedical engineering*, 54(10):1740–1749.
- Fujita, Y., Kojima, H., Hidaka, H., Fujimiya, M., Kashiwagi, A., and Kikkawa, R. (1998). Increased intestinal



$$\begin{aligned} \dot{X}_{s1}(t) &= -k_{gri} \cdot X_{s1}(t) \\ \dot{X}_{s2}(t) &= k_{gri} \cdot X_{s1}(t) - k_{empt} \cdot X_{s2}(t) \\ \dot{X}_g(t) &= k_{empt} \cdot X_{s2}(t) - k_{abs} \cdot X_g(t) \\ \dot{X}_p(t) &= k_{abs} \cdot X_g(t) - k_{elim} \cdot X_p(t) \end{aligned}$$

(b) ODE system

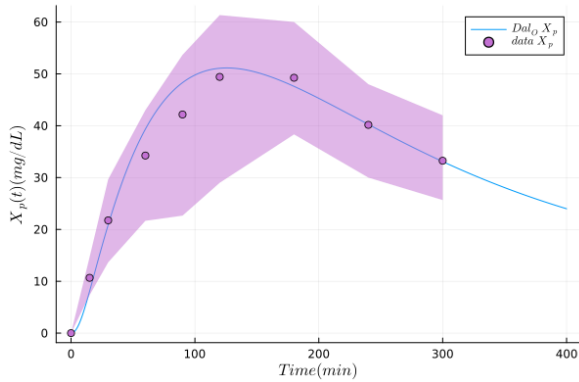
$$\begin{aligned} X_{s1}(0) &= \frac{D_X}{BW \cdot V_{DX}} \\ X_{s2}(0) &= 0 \\ X_g(0) &= 0 \\ X_p(0) &= 0 \end{aligned}$$

(c) Initial conditions

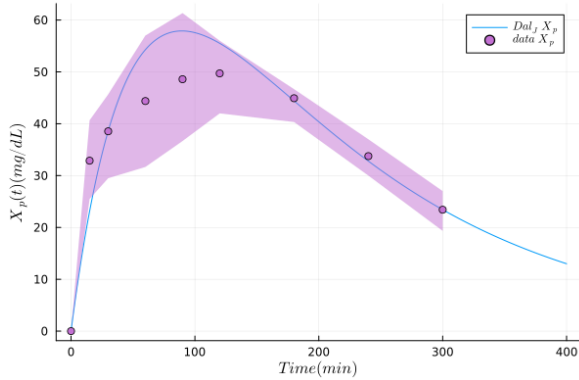
$$k_{empt} = k_{min} + \frac{k_{max} - k_{min}}{2} \left(2 - \tanh \left(\frac{5(X_{s1}(t) + X_{s2}(t)) - b \cdot D_X}{2 \cdot b \cdot D_X} \right) \right) + \tanh \left(\frac{5(X_{s1}(t) + X_{s2}(t)) - a \cdot D_X}{2 \cdot (1 - a) \cdot D_X} \right)$$

(d) Expression of k_{empt}

Figure 9: Model with complex gastric emptying



(a) X_p from oral bolus.



(b) X_p from jejunal bolus.

Figure 10: Results of parameters estimations of dallaman's model on oral and jejunal data.

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.

Sobol', 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.