Connecting sensitivity, identifiability and interpretability of a glucose minimal model

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***Abstract*—Mathematical models have increased their applications in physiology, control and systems science, and biomedical engineering because they offer the opportunity to examine the structure and behavior of complex physiological systems. They provide a concise description of complex dynamic processes, indicating ways to improve experimental design and allowing the testing of hypotheses related to physiological structure. When building a mathematical model, it is important to assess the impact of different factors on the overall behavior of the system being modeled and determine which variables significantly influence the system. Properties such as identifiability, sensitivity, and interpretability in mathematical models are crucial for representing real-world phenomena. In this paper, a sensitivity, structural identifiability, and qualitative parameter interpretability analysis are carried out in a new version of the minimal model of the glucose-insulin system. The aim was to evaluate the structure of this new mathematical model and the existing relationship among sensitivity, identifiability, and interpretability of the model parameters. The findings show that although the model is identifiable, the identifiability analysis can be affected by the lack of interpretability of the parameters, evidencing an important connection between the properties of the model such as sensitivity, structural identifiability, and parameter interpretability, which provide important details about the model structure.**

***Keywords*—Interpretability, parametric interpretability, gray box models, semi-physical models, biotechnological processes.**

I. Introduction

Diabetes mellitus is a metabolic disease that is growing exponentially around the world. Despite notable advances in the treatment of diabetes, patients continue to have difficulty achieving glycemic targets [1]. Different strategies have been proposed to face the challenges in diabetes mellitus treatment. In this regard, mathematical models have played an essential role in the understanding of homeostatic control, analyzing experimental data, identifying and quantifying relevant biophysical parameters, designing clinical trials, and evaluating diabetes prevention or disease modification therapies. One of the most widely used mathematical models in clinical assessments, such as glucose efficiency and insulin sensitivity, is the well-known minimal model proposed by Richard Bergman [2], in which the glucose–insulin system is modeled to offer one of the clearest and simplest examples of homeostatic control in the organism.

In the domain of mathematical modeling, it is extremely important that modelers have confidence in the model they are constructing, regardless of whether the model is a mechanistic or data-driven model. Confidence in a model is strongly related to its properties, such as structural identifiability, parameter sensitivity, and model interpretability. Structural identifiability refers to the ability to find the best unique value of the set of model parameters from the available measurements [3]. It is said that if the model output can faithfully reproduce the measured data, the model is good enough to represent the system and can therefore be trusted. However, in practice, incorrect specification of the model structure and noise data may affect the identifiability of the model parameters [4], and therefore their identification is not guaranteed to be accurate. Interpretability, as a property of the mathematical models, could help parameter identification by adding prior knowledge that can be used to constraint parameter estimation [5], i.e., to narrow the search space/domain of the parameters where the identification procedure operates.

The identifiability property of mathematical models is usually considered a pre-requisite to experiment design, system identification, and parameter estimation [6], [7]. Before performing an identifiability analysis, a sensitivity analysis is useful to understand how model outputs are influenced by variations in model inputs, possible disturbances, or model parameters [8]. Sensitivity analysis can be approached with local and global methodologies. Global sensitivity analysis

allows exploration of the space of possible assumptions and alternative model structure in the model prediction, thus testing both model quality and the robustness of model-based inference [9]. In addition, it contributes to the output uncertainty and fulfills the function of ordering the model parameters according to their relevance in determining the variation in the model outputs. In this work, a sensitivity analysis, a structural identifiability analysis, and a qualitative interpretability analysis have been carried out for a particular model structure of the glucose minimal model. The new form of the minimal model uses the rate of glucose appearance in the portal system calculated by the physiological model of the human gastrointestinal tract reported in [10] and the hepatic glucose production calculated by the liver model reported in [11], as detailed in Section II. A brief theoretical call of each property is introduced in Section III and the results of the analysis of the mentioned properties of the model and the discussion are reported in IV and V, respectively.

II. Mathematical model

An extended version of the glucose minimal model reported in [12] was modified by coupling some estimations from a physiological model representing the gastrointestinal tract, which includes the stomach, the small intestine, and the liver.

The physiological-based model contains three submodels, one for each major organ of the gastrointestinal tract, including the liver. These three organs were modeled knowing the physiological phenomena involved in the glucose homeostasis mechanism that takes place in each one of them and using analogies from the process engineering. The stomach was considered a closed assembly of circular pipes where the heterogeneous mixture flows. However, two reactors and one continuously stirred tank [13] were also considered as the process systems to apply the conservation principle and get the structure of the model. One reactor represents the internal part of the stomach where food is mixed with gastric juices and digested, and the other is the muscular wall where enzymes are produced and glucose combustion occurs. The continuously stirred tank represents the blood supplying the stomach tissue, which carries substances important to the cells in the stomach wall. The small intestine was modeled as a set of stirred tanks, each with an elastic and semi-permeable wall that hypothesizes intestinal peristalsis and the absorption of nutrients into the blood, and connected between them through a valve that regulates the outflow according to the pressure drop between two connected tanks [10]. To model the liver, a continuously stirred tank is considered to represent the liver sinusoid, and a two-zone continuous stirred tank reactor hypothesizes the total amount of hepatocytes in a sinusoid [11]. The main objective of the physiological-based model of the human gastrointestinal tract was to estimate the glucose rate of appearance in the portal vein after a mixed meal and calculate the hepatic glucose production.

The extended minimal model is a two-compartmental model that represents glucose-insulin interactions, considering the triangular meal and insulin subsystems. The first compartment represents the time-varying plasma glucose concentration G and the second compartment predicts a growth rate inversely proportional to the effective insulin concentration in the remote compartment X. The model includes also compartments for oral consumption of carbohydrates and subcutaneous insulin infusion, representing in a good way the pharmacokinetics of the insulin after subcutaneous injection. In this regard, the triangular subsystem considers a first compartment where the insulin is injected I_{sc1}, then the insulin passes to a second compartment I_{sc2} before reaching the plasma. The aim of this model was to create individualized meal disturbance profiles that could be used within a context of a model predictive controller to stabilize blood glucose excursions, anticipate the occurrence of meals, and improve postprandial blood glucose control in people with type I diabetes mellitus.

With the aim to reproduce a blood glucose time series from a continuous glucose monitor (CGM) and show different scenarios of blood glucose variability with an insulin dose calculated by the patient, this extended version of the minimal model was coupled with the gastrointestinal model as follows. The glucose compartment equation was modified by replacing the rate of glucose appearance (Ra) and hepatic glucose production (HGP) estimated by [10] and [11], respectively, leading to Equation 1.

$$\dot{G}(t) = -S_g\, G + \frac{HGP}{\Delta t} - X S_I G + \frac{Ra}{V_g\, BW} \tag{1}$$

In this way, original equations in the extended minimal model with two compartments representing the oral glucose transport in the gastrointestinal submodel and estimating the glucose rate of appearance were not considered in the coupled model. The equations for the insulin compartment remained the original ones in the minimal model as shown in the set of Equations 2.

$$\text{Insulin subsystem} \begin{cases} \dot{X} &= -p_2 X + p_2 (I - I_b) \\ \dot{I}_{sc1} &= -(k_1 + k_d) I_{sc1} + j(t) \\ \dot{I}_{sc2} &= -k_2 I_{sc2} + k_d I_{sc1} \\ \dot{I} &= -nI + \frac{IRa}{V_I \cdot BW} \end{cases} \tag{2}$$

with all the parameters defined by assessment equations, i.e., directly with a numerical value. The parameters are reported in Table I.

III. Model properties

A. Sensitivity

The sensitivity analysis of a mathematical model allows classifying and ranking the model parameters according to their relative influence on the model predictions [14]. This provides valuable information on the practical identifiability of the model by highlighting the parameters that are most strongly correlated, and those that do not significantly affect the model output [15]. This is useful for debugging the mathematical model while facilitating the optimal design of experiments [16]. Local parametric sensitivities $Se^{e}_{\theta_{i,j}}$ are calculated as shown in Equation 3, where e corresponds to

the experiment number, o represents the model output, and θ_i denotes the parameters of the mathematical model.

$$Se^{e}_{\theta_{i,j}} = \frac{\partial {y_j}^{e,o}}{\partial \theta_i}(t_s^{e,o}) \tag{3}$$

The factors of significance (λ_θ), which were introduced in [14], [17], are employed to extract valuable information from the sensitivity calculations. In this context, λ_θ^{msqr}, as depicted in Equation 4, enables the quantification of the model's sensitivity towards a specific parameter.

$$\lambda_{\theta_i}^{msqr} = \frac{1}{n_d}\sqrt{\sum_{mc=1}^{n_{lhs}}\sum_{e=1}^{n_e}\sum_{o=1}^{n_o}\sum_{s=1}^{n_s}\left(s^{e,o}_{\theta_i,j}(t_s^{e,o})\right)^2} \tag{4}$$

where n_e is the number of experiments, n_o the number of observed variables (observable), n_{lhs} the number of samples in the LHS algorithm, n_s the specific sampling time for each experiment with a given observable, $n_d = n_{lhs}n_in_on_s$, and $s^{e,o}_{\theta_i,j}(t_s^{e,o})$ the parameter sensitivity θ_i, with observable j, in experiment e (with sampling time t_s). For the sensitivity analysis of the modified version of the minimal Bergman model, all model parameters were included.

B. Identifiability

The parameter estimation process in semi-physical models based on first principles often faces difficulties that arise mainly from the identifiability that is usually overlooked [18], [19]. Structural identifiability refers to the ability to compute a unique solution for the parameters of a model [20] and can be local or global depending on whether it is satisfied in a specific neighborhood or in the entire parameter space [21]. Although the identifiability property is useful for both parameter estimation and optimal design of experiments, its definition is based on the assumption that one has noise-free experimental data [22]. Several tools are available in the literature to facilitate the calculation and analysis of the structural identifiability property. Some of these tools include SIAN software [23], DAISY software [4], STRIKE-GOLDD software [7], and GenSSI software [18]. In this particular work, the GenSSI software is used to perform the structural identifiability analysis using the series generation method.

The series generation method involves the generation of a system of nonlinear equations involving the model parameters, through the calculation of successive Lie derivatives on these parameters of the mathematical model. This method provides sufficient but not necessary conditions for structural identifiability. Therefore, if the solution of the system of equations is unique, the parameters are globally identifiable in structural terms [14]. Considering the analytical difficulty for the solution of the resulting set of algebraic equations is difficult to solve analytically, we use the tool of identifiability tables proposed by Balsa Canto et al. [14]. The identifiability table is constructed by considering the Jacobian of the coefficients of the series with respect to the set of unknown parameters considered. The Jacobian has as many columns as unknown parameters and as many rows as non-zero coefficients. The identifiability tables and how to interpret them are described in [24].

For the structural identifiability analysis, a realistic scenario was considered in which it is possible to measure only the blood glucose concentration G. In addition, insulin dose ($u_2 = J$) was considered as the input variable. For the particular case of the new version of the Bergman's minimal model, the parameters to be identified are essentially of two types. First, those that, although physiological parameters, are difficult to measure or model in terms of other easily measurable physiological variables (see Equation 5). Secondly, those parameters that have no physical meaning in the context of the application of the mathematical model or whose meaning is strongly linked to the modeling hypothesis used for the derivation of the mathematical model, and whose value is therefore difficult to determine a *priori* (see Equation 6). Considering the above, the identifiability analysis was performed considering the total vector formed by θ_1 and θ_2, and the vector of initial conditions presented in Equation 8.

$$\theta_1 = \begin{bmatrix} S_g & IR_a & R_a & S_I & HGP \end{bmatrix} \tag{5}$$

$$\theta_2 = \begin{bmatrix} k_1 & k_2 & k_d & n \end{bmatrix} \tag{6}$$

$$x = \begin{bmatrix} G & X & I_{sc_1} & I_{sc_2} & I \end{bmatrix} \tag{7}$$

$$x_0 = \begin{bmatrix} 100 & 0 & 358 & 285 & 4.92 \end{bmatrix} \tag{8}$$

C. Interpretability

The interpretability concept has rarely been addressed as a property of mathematical models [25], therefore, as far as the authors know, there is still no consensus so far about how to define, quantify, or measure the interpretability of a mathematical model. The most common approach to interpretability is to improve the level of explanation in machine learning models or black box models. Furthermore, many articles consider interpretability as a property of the modeler, rather than of the model itself, seeking to gender trust and understand the behavior of the model and its results [26]. According to the available literature, when a model is interpretable, the modeler can trust it, being certain that the results given by the model correspond to those of the process of the real object being modeled [25], [27], [28].

Interpretability as a latent property of the model can be influenced by different factors such as the number of features, the complexity of the model, transparency of the model [27], the level of detail, the level of specification, the basic structure of the model [29], and the relationship of the output behavior of the model with the existing physical principles [30]. The interpretability of a mathematical model is also related to the physical meaning of its parameters, i.e., a model is more interpretable the more parameters with real physical meaning it has. In this regard, white-box models have a higher degree of interpretability than black-box models [23]. However, it is possible to furnish interpretability to a gray or black box model through its parameters. The first approximation to provide a model with interpretability is reported in [29] and consists of distinguishing the basic structure of the model from the extended structure and thus obtaining its first level of specification. Once all the functional parameters are known, they must be classified into scalars, coupled, and non-coupled

according to their mathematical definition [29]. The next step is evaluating the functional parameters according to their capability to describe the phenomena occurring in the process under study [29]. In this study, the following classification proposed in [29] is used to analyze the interpretability of the parameters of the new version of Bergman's minimal model:

- General interpretability: *Inherent physical meaning of a model parameter independent of the assumptions used to derive the basic structure of the model.*
- Contextualized interpretability: *Physical meaning of a parameter valid only in a specific mathematical model and dependent on the considerations and hypothesis used to deduce the mathematical model within a given context.*
- Noninterpretability: *The parameter has no physical meaning within the model. Noninterpretable parameters must be then represented by a symbol without an interpretable property in the knowledge domain of the process.*

IV. Results and discussion

A. Sensitivity analysis

In this section, qualitative results are presented for the sensitivity analysis of the new version of the minimal Bergman model, using the importance factor λ_θ^{msqr}. For this purpose, AMIGO toolbox is used to calculate the absolute and relative ranking of the parameters, indicating a descending order of sensitivity. This method uses advanced numerical techniques that cover the full iterative identification procedure. It enables the evaluation of the impact of model parameters on the model output by conducting a sensitivity analysis of its parameters [31]. The objective function selected for the analysis is the variable G, which represents the glucose measurement in blood. The sensitivity coefficients resulting from the sensitivity analysis are shown in Table I. This table displays which parameters have the most significant impact on the model's behavior. It is important to clarify that Δ_T explicitly represents the simulation sampling time and is not the sampling time used by the glucose sensor.

Figure 1 shows the same findings. The left-side figure displays the absolute indices, which represent the global full ranking of the model's parameters. The middle figure presents the global relative ranking values. In both curves, it is possible to visualize the correspondence between the sensitivity coefficient (axis y) and a specific parameter (axis x), ordered in descending order. The results in the figure on the right-hand side show the global MSQR relative sensitivity analysis using heat maps. Visualization using heatmaps facilitates the presentation and interpretation of the results and provides an effective graphical tool to highlight the relative importance of the parameters in the analyzed system.

From the sensitivity analysis, 3 of the 15 parameters of the model have an index equal to zero. This implies that these parameters do not affect or are not related to the output of the model, changes or variations in this set of parameters have no impact on the model response. It is also observed that the parameters S_g and S_I have significant absolute and relative sensitivity, indicating that their values are relevant to the model's output. However, according to the heat map, the parameters that have the greatest impact on the model's output are HGP and Δ_T because their relative sensitivity indices are the highest.

Tabla I
Sensitivity coefficients of the parameters of the new version of Bergman's minimal model (in descending order).

Parameter	Description	Relative λ	Absolute λ
HGP	Hepatic glucose production.	5.24×10^{-2}	4.11×10^{-1}
Δ_T	Simulation sampling time.	5.24×10^{-2}	8.63×10^{-1}
S_g	Fractional glucose effectiveness.	3.78×10^{-2}	8.61×10^{1}
n	Rate constant.	2.35×10^{-2}	5.55
S_I	Insulin sensitivity.	2.28×10^{-2}	1.84×10^{3}
IR_a	Insulin rate of appearance in plasma.	2.28×10^{-2}	4.78×10^{-2}
V_I	Distribution volume of insulin.	2.28×10^{-2}	1.43×10^{1}
BW	Body weight.	1.93×10^{-2}	1.14×10^{-2}
R_a	Glucose rate of appearance in the portal system.	4.55×10^{-3}	2.46×10^{-2}
V_g	Distribution volume of glucose.	4.55×10^{-3}	7.49×10^{-2}
p_2	Rate constant of the remote insulin compartment.	3.25×10^{-3}	6.93
I_b	Basal insulin.	9.12×10^{-4}	3.81×10^{-2}
k_1	Rate constant of nonmonomeric insulin absorption.	0	0
k_2	Rate constant of nonmonomeric insulin absorption.	0	0
k_d	Rate constant insulin dissociation.	0	0

B. Identifiability analysis

The structural identifiability analysis of the new version of Bergman's minimal model was performed as described in Section III-B. It took 4 Lie derivatives to complete the structural identifiability analysis. The identifiability table turned out to be of incomplete rank ($R = 5$) so the model, considering the parameters presented in Equations 5 and 6 as unknown, is structurally unidentifiable.

Figure 2 shows the identifiability charts generated with the Genssi software. Figure 2(a) corresponds to the general identifiability table, in which all the parameters considered for the analysis appear. As can be seen in the figure the parameters k_1, k_2, and k_d have a value of zero in the table, which means that it was not possible to find a unique solution for the parameter neither in general nor in a neighborhood, so the parameters turned out to be structurally unidentifiable. On the other hand, Figure 2(b) corresponds to the reduced identifiability tableau, resulting from eliminating the unidentifiable parameters and recalculating the necessary relations to find a solution to the problem of identifying the remaining parameters. Finally,

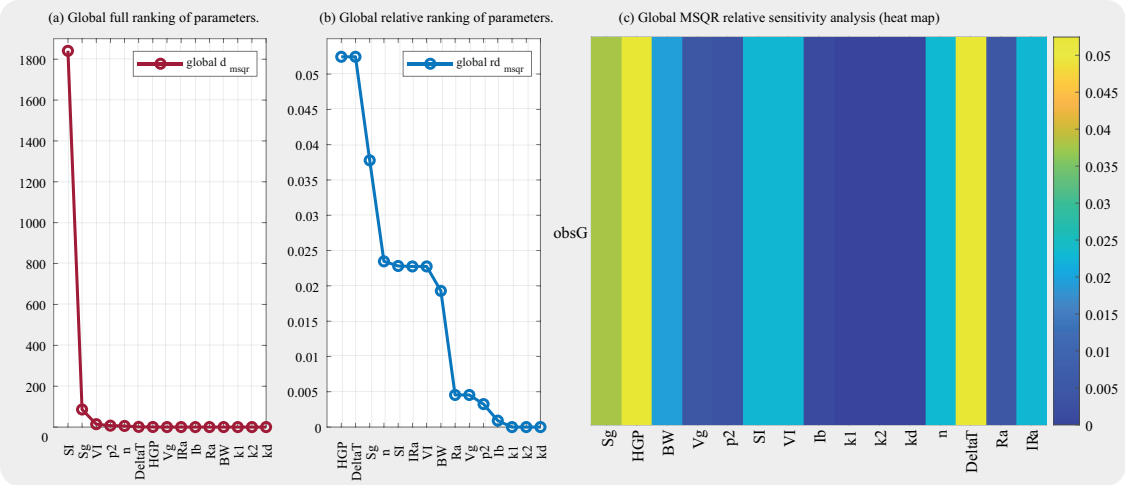


Fig. 1. Global sensitivity analysis using the AMIGO toolbox [31].

Figure 2(c) shows those parameters for which the analysis was not conclusive in terms of their structural identifiability. The parameter S_I can be described in terms of two or more coefficients of the Lie derivatives, with a single solution, so it is considered structurally globally identifiable (SGI).

C. Parameter interpretability analysis

Model interpretability is not an on-off property, its evaluation requires grading a model on a scale that requires a metric to quantify the interpretability in a mathematical model [29]. In this study, an interpretability analysis of the model described in Section II is presented from a qualitative point of view, given the interpretability of its parameters.

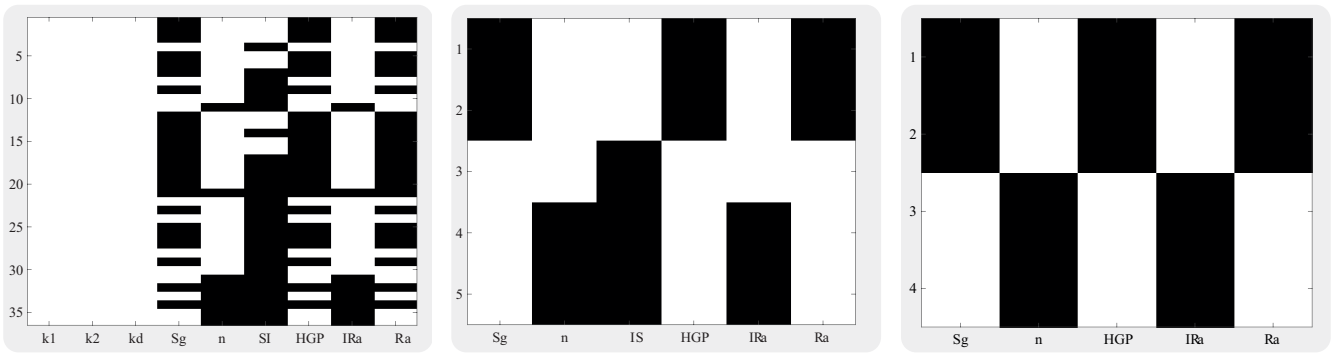
Tabla II
INTERPRETABILITY ANALYSIS OF THE PARAMETERS OF THE MODIFIED VERSION OF BERGMAN'S MINIMAL MODEL.

Interpretability classification	**Parameter**
General	BW
Contextualized	V_g, R_a, S_I, V_I, IR_a, HGP, I_b
Noninterpretability	n, p_2, S_g, k_1, k_d, k_2

In the modified version of Bergman's minimal model, the zero specification level is hidden, meaning that the model's basic structure is not reported in a way to easily distinguish it from the extended structure. In this case, it is hard to classify the parameters as structural or functional. Based on that, we consider the scenario in which all parameters belong to the first specification level, i.e., all are considered structural and are defined directly by a numerical value. As can be seen in Equations 1 and 2, the set of differential equations originated from balances between two compartments declared by the authors [12]. In this version of the minimal model, all parameters are defined directly with a numeric value, which leads to a non-existent extended structure of the model and a classification of the parameters as scalars. A qualitative evaluation of the interpretability of the parameters is reported in Table II. It's unsurprising that as a result non-interpretable parameters (k_1, k_2, and k_d) have no sensitivity and indeed the same parameters cannot be identified. It suggests that determining a particular set of parameters that allows the model to reflect the dynamics of the modeled system cannot be uniquely resolved. Moreover, the identifiability analysis is affected by the lack of interpretability of these parameters, as it is hard to set maximum and minimum values for them if their physical meaning is unknown. On the other hand, among the parameters with contextualized interpretability (S_I, Ra, IR_a, HGP), there is the parameter with the highest absolute sensitivity coefficient (S_I) which, although it is a physiological parameter that is difficult to measure, is the only globally structural parameter identifiable. The other parameters do not provide a clear result, indicating that the model's structure may need to be adjusted to increase its interpretability in terms of parameters. If those parameters become interpretable and interpretability is considered a property of the model, it is likely that the identification of the parameters will be facilitated with prior information about the modeled system, and the descriptive capacity of the model itself can be exploited.

V. CONCLUSIONS

The structure of the mathematical model can be significantly improved with the information provided by the intrinsic properties of the model, such as sensitivity, identifiability, and interpretability of its parameters, but these properties can also be helpful for the optimal design of experiments and improve the model-user interaction. After analyzing the new version of Bergman's minimal model, it became clear that these three properties are closely linked and offer valuable insights into the model structure. In this regard, it is important to continue researching and developing a formal framework for the concept of interpretability. This would create a reliable metric for evaluating the grade of interpretability of mathematical models. This, in turn, would help shed light on the identifiability of the model being analyzed.



(a) Identifiability table with parameter vectors θ_1 and θ_2.

(b) Reduced identifiability tableau 1

(c) Reduced identifiability tableau 2

Fig. 2. Identifiability tableaus for the coupled Bergman minimum model obtained using GenSSi software [18].

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