Low–Order Nonlinear Animal Model of Glucose Dynamics for a Bihormonal Intraperitoneal Artificial Pancreas

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***Abstract*— Objective: The design of an Artificial Pancreas (AP) to regulate blood glucose levels requires reliable control methods. Model Predictive Control has emerged as a promising approach for glycemia control. However, model–based control methods require computationally simple and identifiable mathematical models that represent glucose dynamics accurately, which is challenging due to the complexity of glucose homeostasis. Methods: In this work, a simple model is deduced to estimate blood glucose concentration in subjects with Type 1 Diabetes Mellitus (T1DM). Novel features in the model are power–law kinetics for intraperitoneal insulin absorption and a separate glucagon sensitivity state. Profile likelihood and a method based on singular value decomposition of the sensitivity matrix are carried out to assess parameter identifiability and guide a model reduction for improving the identification of parameters. Results: A reduced model with 10 parameters is obtained and calibrated, showing good fit to experimental data from pigs where insulin and glucagon boluses were delivered in the intraperitoneal cavity. Conclusion: A simple model with power–law kinetics can accurately represent glucose dynamics submitted to intraperitoneal insulin and glucagon injections. The reduced model was found to exhibit local practical as well as structural identifiability. Importance: The proposed model facilitates intraperitoneal bi-hormonal model-based closed-loop control in animal trials.**

***Index Terms*— Artificial pancreas (AP), power–law kinetics, model validation, parameter identification.**

Manuscript received November 9, 2020; revised January 28, 2021 and September 15, 2021; accepted October 25, 2021. Manuscript received in final form on November 3, 2021. Date of publication XXXXXXX XX, XXXX. Claudia Lopez-Zazueta was supported by ERCIM 'Alain Bensoussan' Fellowship Programme at the Norwegian University of Science and Technology (NTNU). This research is also funded by The Norwegian Research Council (Project no.: 248872/O70), Central Norway Regional Health Authority, and Johan Selmer Kvanes Endowment for Research and Combating of Diabetes. *(Corresponding author: Claudia Lopez-Zazueta)*

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I. Introduction

Type 1 Diabetes Mellitus (T1DM) is the condition resulting from a deficiency in the production of insulin from β–pancreatic cells. A common therapy to control this disease consists of exogenous insulin infusions given several times per day. Insulin injections have to be controlled to some extent manually, which is a laborious task and a major concern for people with T1DM and their families [1], [2].

In order to help patients with T1DM, the idea of a fully–automated Artificial Pancreas (AP) has been studied for decades [3]. Basically, an AP is a device that uses blood glucose measurements (collected with a sensor from a subject) in a decision–making algorithm that estimates the necessary amount of insulin to be administered in the subject [2]. The quantity of insulin to be infused must be precisely calculated in order to keep glucose levels in a safe and optimal range [1]. Additionally, glucagon infusions can be used to counteract severe hypoglycemia [4], [5].

AP can be classified in hybrid or fully–automated AP systems. Hybrid systems demand the user to announce known disturbances (e.g. meals, physical activity, etc.), while for fully–automated AP the subject does not need to take part in the control [6]. A fully–automated AP is expected to provide a better control and reduce hyperglycemia and hypoglycemia occurrences [7]–[9].

However, the slow insulin absorption is one obstacle to achieve stable and safe control of blood glucose levels. For instance, in the case of subcutaneous insulin infusions there is a significant delay of insulin transport through the subcutaneous tissue. Then, to keep glucose levels within a target range, the patient is required to announce in advance events such as the ingestion of meals with an estimation of carbohydrate contents or physical activities [1], [2]. Nevertheless, this relies on the ability of the patient to announce events, which is cumbersome to repeat multiple times per day and patients struggle to properly estimate meal content.

Consequently, a fully–automated AP would be of great help to any patient and, if its operation is accurate, it could improve the control of blood glucose levels compared to manual glucose regulation. However, there are still problems to face and efforts must be made to achieve a fully–automated AP.

The control of blood glucose concentration in T1DM is a challenging problem because of the complex, non–linear, and

time–varying dynamics of glucose homeostasis [2], including delays in insulin infusions [1], inter and intra–subject variability [10], [11], etc. Model Predictive Control (MPC) has emerged as a promising approach for the control of blood glucose levels [12]. Effective MPC requires an accurate and individualized model of patient glucose–insulin dynamics [13]. However, the identification of such models is a tough task and the methods to measure individual parameters are invasive and expensive [8].

Several proposed models attempt to describe the glucose metabolism in some detail [14]–[16], and are thus useful for simulating glucose dynamics. However, these nonlinear, high–order models have a large number of parameters that in general cannot be identified from easily obtainable data [12]. Moreover, their usage in MPC is computationally demanding, making their integration on an AP impracticable [8] and does not assure a better closed loop control [9].

In contrast, it has been shown that low–order linear models with parameters estimated from clinical data can be suitable for MPC with subcutaneous insulin delivery [17]. However, more computationally tractable, minimalistic, and rather linear models [18]–[21] often do not represent well the non–linear dynamics that have been seen after intraperitoneal insulin infusions [22].

The purpose of this article is to present a relatively simple nonlinear model to approximate T1DM glucose dynamics when insulin and glucagon boluses are introduced in the intraperitoneal (IP) cavity. The conception of a new model is also motivated by the fact that most of the work developed for AP systems is adapted to subcutaneous insulin delivery [23].

A tight glycemic control is difficult to attain with an AP operating with subcutaneous insulin infusion, due to delays in insulin absorption and slow insulin–clearance rates [1], [23]. For these reasons, the intraperitoneal route to infuse insulin has been investigated, since insulin–glucose kinetics are significantly faster in the IP cavity than subcutaneously [23], [24]. Furthermore, it has been observed that blood glucose increases faster when glucagon is delivered in the IP cavity, compared with subcutaneous glucagon infusions [5].

Therefore, the problem of not having a stable and safe control due to the slow subcutaneous hormone (insulin and glucagon) absorption can be overcome with an intraperitoneal AP, because the delay of hormone absorption would be considerably reduced.

In addition, a small identifiable model to predict blood glucose dynamics during intraperitoneal insulin and glucagon infusions is required for future experimental purposes. The objective is to calibrate the model with subcutaneous glucose measurements and / or intravenous (IV) blood samples analyzed on a blood gas machine [5], [25], [26] from the first 2–3 hours of an experiment, to obtain a personalized model and then decide a model–based controller to normalize blood glucose during the rest of the animal trial using intraperitoneal boluses. This implies that the parameters of the model have to be estimated as fast as possible, in order to test the control method throughout the rest of experiment (which, with anesthetized pigs, may last for not more than 10–12 hours).

This basic procedure will mimic the operation of an AP, which requires a model feasibly adaptable (i.e. a model that can be personalized) to the glucose dynamic scenario of a determined time frame. Additionally, having a simple model that can be adapted multiple times a day will allow for intra–subject variability to be addressed.

In order to elucidate whether and how the proposed model can be simplified, its local practical and structural parameter identifiability has been analyzed. Parameter profile likelihoods as well as a method based on Singular Value Decomposition (SVD) of the sensitivity matrix have been used. The analysis has led to detect non–identifiable parameters and to define a reduced model with less parameters to estimate, while keeping a satisfactory accuracy when approximating blood glucose measurements.

The paper is organized as follows: In Section II, a model to describe T1DM glucose dynamics is introduced. The model accounts for intraperitoneal infusion of insulin and glucagon, as well as for an exogenous IV glucose input. In Section III, a reduced model to describe T1DM glucose dynamics is presented. The parameter identification analysis of the reduced model is also exposed. In Section IV, the experiments from where glucose data were obtained are described, as well as the method to calibrate the model with the data. In Section V, the results obtained after calibrating the reduced model are shown. Finally, the discussion and conclusion about the work are exposed in Sections VI and VII, respectively.

II. Bihormonal–Glucose Model

In this Section, a model to simulate T1DM glucose dynamics is described. This model accounts for insulin and glucagon boluses introduced in the IP cavity. The model is based on two different models, which were deduced to approximate experimental data from experiments with either intraperitoneal insulin boluses, or intraperitoneal and subcutaneous glucagon boluses. These two initial models are presented in Supplementary material S.1 and Supplementary material S.2

The bihormonal–glucose model is the following:

$$\begin{aligned}\frac{dG}{dt} =& -\left[k_1 + k_I \cdot (I + I_b) + k_{i_1} \cdot i_1\right] \cdot G \\ &+ k_H \cdot (H + H_b) \cdot \xi + r_G \cdot Ra_G \end{aligned} \tag{1}$$

$$\frac{dI}{dt} = - m_1 \cdot I + m_2 \cdot i_1^p \tag{2}$$

$$\frac{di_1}{dt} = -m_3 \cdot i_1^q + m_4 \cdot i_2 \tag{3}$$

$$\frac{di_2}{dt} = - m_4 \cdot i_2 + u_I \tag{4}$$

$$\frac{dH}{dt} = - n \cdot H + n_2 \cdot h_1 \tag{5}$$

$$\frac{dh_1}{dt} = - n_1 \cdot h_1 + u_H \tag{6}$$

$$\frac{d\xi}{dt} = - x_1 \cdot H \cdot \xi + x_2 \cdot G \cdot I \tag{7}$$

The states, inputs, and parameters of the bihormonal–glucose model (1)–(7) are described in Table I.

In the bihormonal–glucose model (1)–(7), glucose consumption can be insulin-independent with rate $k_1 \cdot G$, or insulin-dependent relying on insulin states I and i_1. On the other

TABLE I

DESCRIPTION OF THE STATES, INPUTS, AND PARAMETERS OF THE BIHORMONAL–GLUCOSE MODEL (1)–(7) AND THE REDUCED BIHORMONAL–GLUCOSE MODEL (8). BLOOD GLUCOSE CONCENTRATION IS THE ONLY OUTPUT OF THE SYSTEM AND THE REST OF STATES ARE CONSIDERED DIMENSIONLESS. ABBREVIATIONS: CS: CIRCULATORY SYSTEM; IC: INTERMEDIATE COMPARTMENT; IP: INTRAPERITONEAL CAVITY; IV: INTRAVENOUSLY.

Description	State	Units	Compartment
Blood Glucose	G	mmol/L	CS
Blood Insulin	I	dimensionless	CS
Insulin IC	i_1	dimensionless	IC
Insulin IP	i_2	dimensionless	IP
Blood Glucagon	H	dimensionless	CS
Glucagon IP	h_1	dimensionless	IP
Glucagon sensitivity	ξ	dimensionless	IC
Input			
Exogenous Glucose infusion IV	Ra_G	mmol/h	CS
Insulin IP bolus	u_I	U	IP
Glucagon IP bolus	u_H	μg	IP
Parameter			
Blood Insulin basal value	I_b	dimensionless	CS
Blood Glucagon basal value	H_b	dimensionless	CS
Insulin–independent removal rate of glucose	k_1	1/d	CS
Insulin–dependent removal rates of glucose	k_I, k_{i_1}	1/d	CS
Exogenous glucose rate of appearance	r_G	h/(L· d)	CS
Glucose response to glucagon rate	k_H	1/d	CS
Consumption, degradation, and transport rates	m_1, m_2 $m_3, m_4,$ n, n_1, n_2	1/d	CS, IC, IP
Decrease rate of glucagon sensitivity	x_1	1/d	IC
Restoration rate glucagon sensitivity	x_2	L/(mmol· d)	IC
Powers	p, q	dimensionless	CS, IC

hand, the increase in blood glucose concentration is regulated by glucagon levels H and the exogenous IV glucose input Ra_G.

The several insulin and glucagon states account for the transport of each hormone through different compartments, from the IP cavity (where the hormone boluses are released) to the circulatory system. The infusion of exogenous insulin and glucagon is represented by the external inputs u_I and u_H, respectively.

In the model it is assumed that the transport of insulin between compartments is nonlinear. This assumption was made based on experimental data [25]. For more details see [22] and Section Supplementary material S.1. This was described in (2) and (3) with power–law kinetics, including the exponents p and q.

Power–law approximation or synergistic systems (S–systems) are used to describe in a non canonical form reactions with particular non–linearities [27]–[29]. The power–law formulation accounts for the change rate of a state as the difference of two products of states raised to non–integer powers [29]–[31]. In this work, given the uncertainty of insulin concentration in compartments where measurements cannot be non–invasively obtained, power–law was used to simulate insulin dynamics using few parameters and simple equations.

According to experimental data where glucagon boluses were administered in the IP cavity and subcutaneously [26], the changes in blood glucose concentration induced by glucagon boluses are not always linearly proportional to bolus sizes (see Section Supplementary material S.2). For this reason, the state ξ to represent the sensitivity to glucagon boluses is included in (7). Since glucagon sensitivity might be linked to the amount of glycogen store in the liver or to the hepatic responsivity to glucagon [32], it is assumed that glucagon sensitivity decrease is proportional to glucagon concentration and it can be restored when glucose is stored in the liver in presence of insulin. For more details about the bihormonal–glucose model (1)–(7) see Supplementary material S.3.

III. REDUCED BIHORMONAL–GLUCOSE MODEL

The reduced bihormonal–glucose model (8) is

$$\begin{aligned}
\frac{dG}{dt} =& -\left[k_1 + \overline{k_{i_1}} \cdot \overline{i_1}\right] \cdot G \\
&+ \overline{k_H} \cdot \left(\overline{H} + \overline{H_b}\right) \cdot \overline{\xi} + r_G \cdot Ra_G \\
\frac{d\overline{i_1}}{dt} =& -\overline{m_3} \cdot \overline{i_1}^{q} + i_2 \\
\frac{di_2}{dt} =& -m_4 \cdot i_2 + u_I \\
\frac{d\overline{H}}{dt} =& -n \cdot \overline{H} + h_1 \\
\frac{dh_1}{dt} =& -n_1 \cdot h_1 + u_H \\
\frac{d\overline{\xi}}{dt} =& -\overline{x}_1 \cdot \overline{H} \cdot \overline{\xi} + G \cdot \overline{i_1}
\end{aligned} \tag{8}$$

The reduced bihormonal–glucose model (8) is a reduced version of the bihormonal–glucose model (1)–(7) presented in II. It is obtained following the transformations to address the lack of local structural and practical identifiability, which are described in Supplementary material S.8 and Supplementary material S.9. The reduced model accounts for 6 states and 10 parameters (1 state and 6 parameters less than the complete model).

The reduced bihormonal–glucose model (8) is validated using experimental data from pigs where insulin and glucagon boluses were administered in the IP cavity. The details are presented in the next two sections. Furthermore, the local practical and structural parameter identifiability of the reduced bihormonal–glucose model (8) were analyzed as explained in Section III-A and Section III-B.

A. Profile Likelihood of the reduced bihormonal–glucose model

Profile likelihoods [33] were computed for the reduced bihormonal–glucose model (8) using the method described in Supplementary material S.5. The results are depicted in Fig. 1. All profile likelihoods have a single minima and exceed the confidence threshold twice. Therefore, no parameters of the reduced bihormonal–glucose model (8) with lack of local practical identifiability were found.

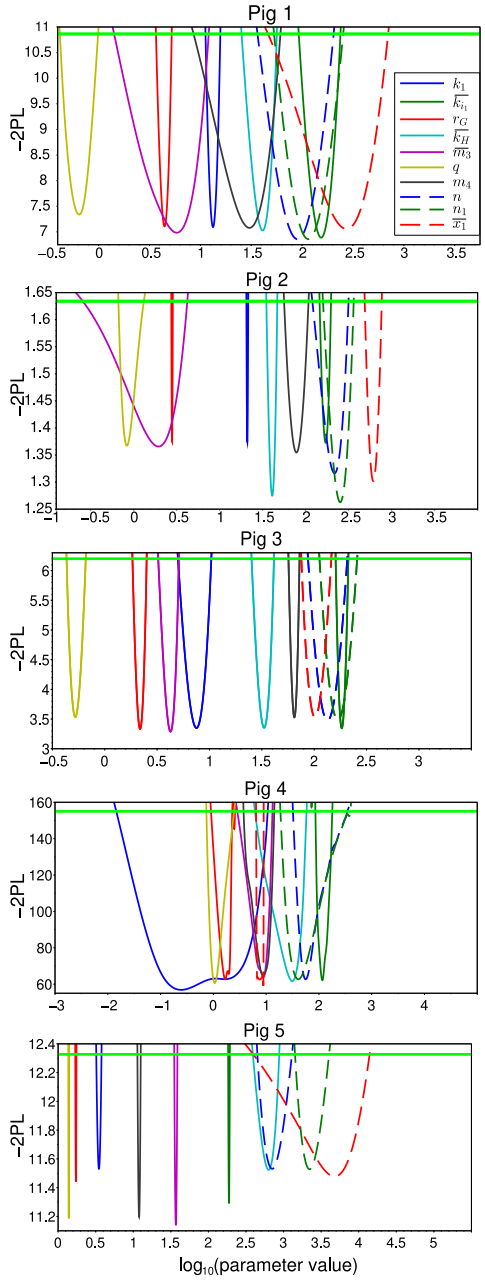

Fig. 1. Profile likelihoods of the reduced bihormonal–glucose model (8). The parameters have profile likelihoods with single minima and that exceed the confidence threshold twice, which suggests that they are locally practically identifiable. The green horizontal lines indicate the confidence thresholds of 99% for Pig 1, 98% for Pigs 2,3, and 4, and 96% for Pig 5.

B. Singular Value Decomposition of the reduced bihormonal–glucose model

The Singular Value Decomposition method [34], [35] described in Supplementary material S.6 was performed for the reduced bihormonal–glucose model (8) combining cases. The result are depicted in Fig. 2. All singular values has order superior to 10^{-6}, while for the bihormonal–glucose model (1)–(7) there are singular values with order 10^{-9} or less. In conclusion, no parameter with lack of local structural identifiability was found for the reduced bihormonal–glucose model (8).

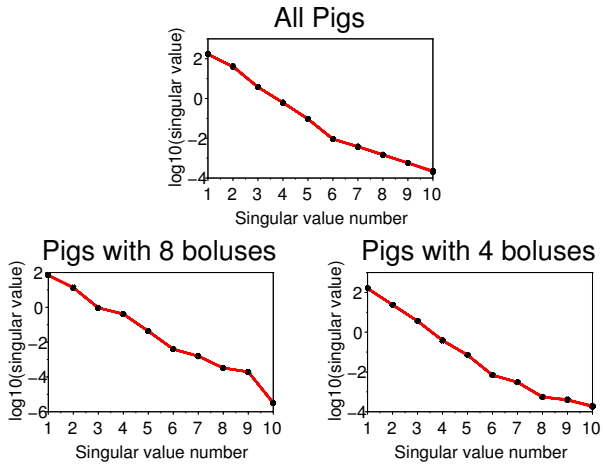

Fig. 2. Singular Value Decomposition of the reduced bihormonal–glucose model (8). No singular value equal to zero or very small was found, suggesting that parameters are locally structurally identifiable.

IV. Data Collection and Methods

A. Data Collection

The reduced bihormonal–glucose model (8) was calibrated using data from experiments with pigs. Each experiment was carried out in about 8 hours. Blood glucose levels were measured at least every 5 minutes from IV blood samples collected in syringes and analyzed on a Radiometer ABL 725 blood gas analyzer (Radiometer Medical ApS, Brønshøj, Denmark) [5], [25], [26].

Glucose was intravenously infused at different rates during all the experiment. In order to simulate food intake, glucose infusion was increased and then decreased as a step function after the first half of the experiments (glucose infusion is depicted in Fig. 3). In the experiments for Pig 1 and Pig 4, there were several increments in glucose infusion to avoid hypoglycemia.

Insulin and glucagon boluses were pumped into the IP cavity. Porcine insulin and glucagon endogenous production were neglected for modeling, since they were suppressed by a combination of octreotide and pasireotide during the experiments.

B. Parameter Estimation: Minimization Method

Model calibration is performed in order to personalize the reduced bihormonal–glucose model (8) for each subject. Parameter estimation for each experiment was carried out using the Nelder–Mead algorithm to minimize the sum of square errors between the model and experimental data. The *fminsearch* tool was used in Scilab to obtain parameter values that minimize the cost function

$$F(\boldsymbol{\theta}) = \sum_{t \in T_{BGA}} \left[BGA(t) - G(t, \boldsymbol{\theta}) \right]^2,$$

where $\boldsymbol{\theta}$ is the vector of parameters to be estimated, $BGA(t)$ blood glucose measurements, T_{BGA} the set of time–points at which glucose was measured, and $G(t, \boldsymbol{\theta})$ the glucose state of the reduced bihormonal–glucose model (8) with the parameters in $\boldsymbol{\theta}$.

After the calibration, the Mean Square Error was computed for each experimental case:

$$\hat{\sigma}^2 = \frac{\sum_{t \in T_{BGA}} \left[BGA - G(t, \boldsymbol{\theta})\right]^2}{n},$$

where n is the sample size.

To compare the accuracy of the model estimation, the BIC (Bayesian information criterion) value was calculated for each experiment case. BIC criterion considers the complexity of the model, i.e. the number of parameters and the sample size. The BIC value is defined as

$$BIC = n \cdot \log(\hat{\sigma}^2) + p_{\#} \cdot \log(n)$$

where $p_{\#}$ is the number of parameters. BIC can take negative values. The better the performance of the model, the lower the BIC value [36].

The parameters estimated are in Table II. For the measurable state (i.e. glucose state), the initial condition can be taken as the last data point registered. For the non–measurable states (dimensionless states), the initial conditions are fixed and not estimated with the minimization method, because they can be readjusted by a change of variable without affecting the output of the system (the measurable state).

A second algorithm based on the quasi–Newton method was used to calibrate the parameters of the reduced bihormonal–glucose model (8). The results are presented in Table S.6 of Supplementary Material S.10. The estimates obtained with the Nelder–Mead algorithm and the quasi–Newton method are close. The mean of the relative difference between the parameters is 0.11.

V. Model Calibration Results

The reduced bihormonal–glucose model (8) is personalized according to the experimental data of each subject. For this purpose, its parameters were estimated for each experimental case, as explained in Section IV. The numerical results are plotted in Fig. 3.

The BIC values for 4 out of the 5 experimental cases are -47.97 in average (see Table II), which suggest that data are accurately approximated with a model of adequate complexity. The case with the largest BIC value (Pig 4) had an abnormal late and sharp response to the first glucagon bolus.

The variability of parameters between individuals is due to the inter–subject variability of glucose dynamics [10], [11]. To determine the range of variation for the parameters will require many experimental cases (which might only be possible with clinical cases) to make the estimations statistical meaningful.

The Mean Square Error between the data and the model was computed for the complete and reduced model. This show that the error obtained approximating the data with the reduced model is lower than with the complete model (compare Table II and Table S.3 of Supplementary material S.4.

Furthermore, the BIC criteria was used to compare the performance of the complete and reduced models to approximate the data of the full experiments (i.e. about 8 hours). BIC values are lower for the reduced model than for the complete model (see Table II and Table S.3 of Supplementary material S.4.), indicating that the reduced model has a better performance for approximating the experimental data. This is shown with the number of cases had at the moment when the work was done. To consider more experimental cases or longer experiments may be done in future works.

TABLE II

Parameters estimated with the Nelder–Mead algorithm for the reduced bihormonal–glucose model (8), parameter Coefficient of Variation (CV), Mean Square Error (MSE), and BIC values of the model approximation. The better the model performance to approximate the data, the lower the MSE and BIC values.

Parameter	Pig 1	Pig 2	Pig 3	Pig 4	Pig 5	CV
k_1	13.79	21.56	7.41	0.98	3.92	0.87
k_{i_1}	171.68	168.68	181.79	115.36	185.46	0.17
k_H	38.50	44.02	33.20	28.63	655.46	1.73
r_G	4.73	2.79	2.21	1.77	1.73	0.47
m_3	4.83	2.33	4.38	8.74	37.89	1.28
m_4	27.84	85.05	64.96	9.49	12.30	0.84
q	0.48	0.81	0.52	0.96	1.37	0.44
n	110.34	177.30	142.24	37.85	709.33	1.15
n_1	138.95	200.09	177.44	38.52	2152.87	1.67
x_1	237.39	196.85	102.37	0.0014	3392.80	1.86
MSE	0.30	0.54	0.36	3.45	0.25	
BIC	-57.40	-8.15	-38.47	174.15	-87.85	

VI. Discussion

The bihormonal–glucose model (1)–(7) and the reduced bihormonal–glucose model (8) have been presented in this work. Both models can be personalized to represent glucose nonlinear dynamics when intraperitoneal insulin and glucagon boluses are administered. Furthermore, these models can represent the variants in glucose infusions as performed during the experiments, leading to conclude that the models can approximate the dynamics of glucose even when there is food intake.

The local identifiability of the complete model was addressed. After local structural identification analysis, the reduction of the bihormonal–glucose model was accomplished through re–parametrization and state transformations. Moreover, a structural identification analysis was performed for the reduced bihormonal–glucose model (8) and no parameter was found to lack of local structural identifiability.

To address practical identifiability of the complete model, two insulin states active in glucose removal were reduced to a single state, and it has been shown that this does not imply less accuracy in the approximation of glucose measurements. Moreover, parameter profile likelihoods were computed for the reduced bihormonal–glucose model (8) and the results suggest that parameters are locally practically identifiable.

In this way, the number of parameters to be estimated was reduced for the bihormonal–glucose model (1)–(7), obtaining the reduced bihormonal–glucose model (8) which can represent experimental data with the same or better accuracy.

The reduced model was inferred taking into account that insulin and glucagon are not measured (to approximate insulin and glucagon measurements, the complete model may be used). Indeed, the reason for reducing is to have a simpler model which can be quickly calibrated after 2–3 hours of animal experiments where only blood glucose measurements are available, so that the model can be tested in MPC.

This article has been accepted for publication in a future issue of this journal, but has not been fully edited. Content may change prior to final publication. Citation information: DOI 10.1109/TBME.2021.3125839, IEEE Transactions on Biomedical Engineering

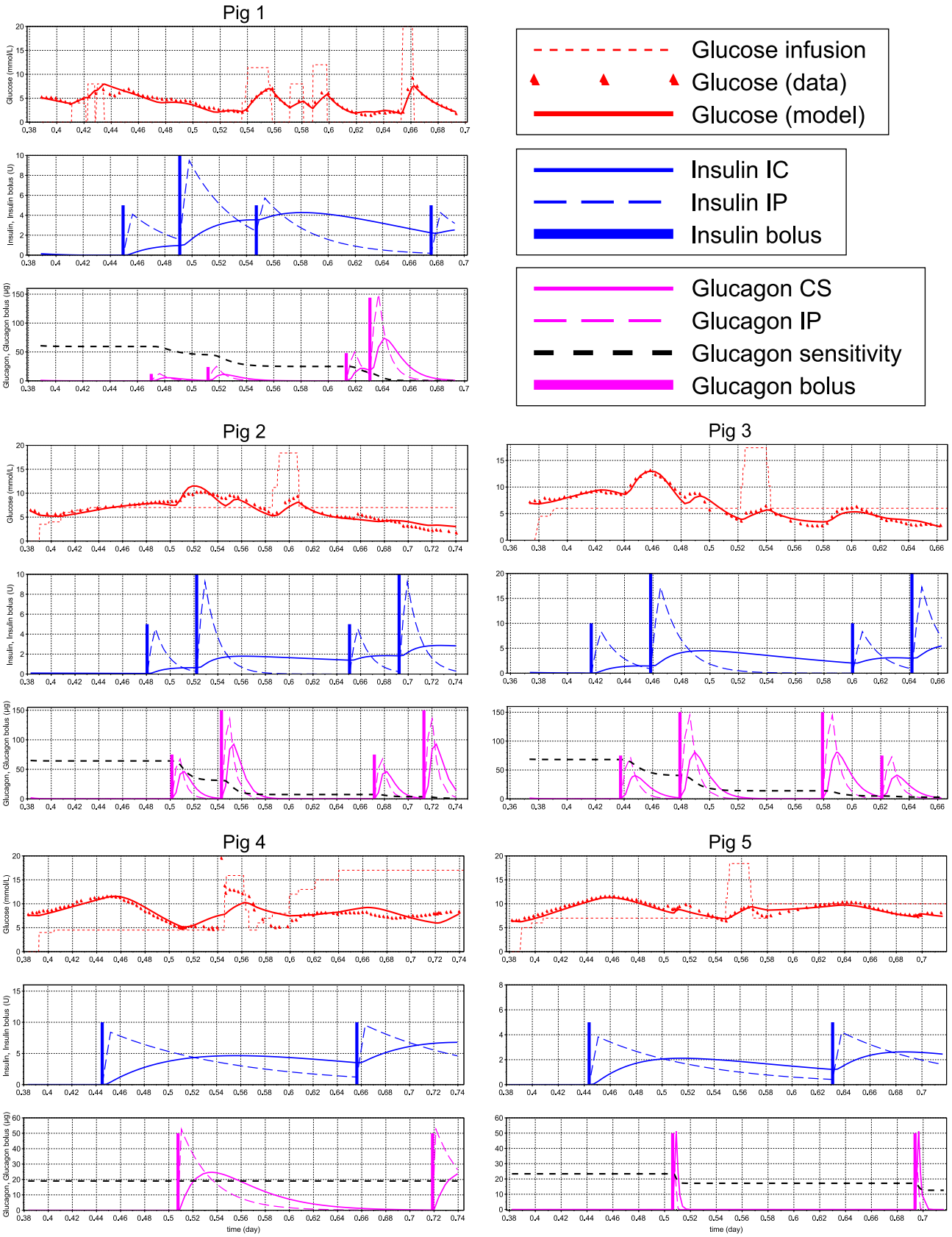

Fig. 3. Reduced bihormonal–glucose model (8) compared to experimental data. During the experiments, several intraperitoneal insulin and glucagon boluses were used to identify the nonlinear dynamics of both hormones and the glucose response. The parameters estimated are described in Table II.

In this work, two different methods were used to address parameter estimation: a minimization routine based on the Nelder–Mead algorithm and the quasi–Newton method. Other approaches can be tested to identify the models with prior knowledge on model parameters, for instance, using Bayesian methodologies [32], [37] and Markov chain Monte Carlo techniques [38], [39].

New technologies concerning the treatment of T1DM have been proposed to be incorporated in AP, for instance, to analyze body sounds to detect meal ingestion [40], [41]. But so far for this work, it is considered that only blood glucose measures will be available and that the information about glucose input is given. Besides, there is low probability that the necessary data to make practically identifiable the parameters of the bihormonal–glucose model could be obtained from a non–invasive device, specially for the parameters related to the concentration of hormones within the intraperitoneal cavity.

Also, glucagon sensitivity might be related to the glycogen stored in the liver and the generation of glucose from amino acids (gluconeogenesis) [42]. As future work, the formulation of the glucagon sensitivity state can be revised, for instance to analyze if in larger periods of time there is an increment in this state and whether there is saturation. In these experiments, the repletion of glycogen in the liver could not be observed, probably due to the short duration of the experiments. However, it is expected that hepatic glycogen repletion will enhance the effects of glucagon doses [43].

On the other hand, the main risks observed in the use of IP insulin infusions are skin infections and interruption of the insulin supply attributable to catheter obstruction [23], [44]–[46]. The addition of a second hormone (glucagon) does not necessarily imply a second port, but rather a single catheter with two channels. Therefore, increasing one to two intraperitoneal hormones may not significantly increase the risk of infection. Even if the efficiency of a single port (or a two–lumen catheter) to infuse dual hormones intraperitoneally is still to be established, the primary purpose of this work is to propose a suitable and relatively simple model to develop a controller that allows progress in animal experiments and future clinical trials.

Although the risk of these complications has been reduced with experience [23], the use of the intraperitoneal route is something that must be balanced with its benefit [47]. In–silico comparisons have shown that with intraperitoneal insulin infusions glucose levels can be controlled within the normal range by giving smaller glucose excursions after meals compared to subcutaneous insulin infusions, keeping blood glucose levels lower and preventing hypoglycemia even without the need for boluses before meals. [45], [48].

Furthermore, in animal experiments it has been observed that, compared to subcutaneous administration of hormones, intraperitoneal boluses induce faster effects on glucose levels while reducing the concentration of hormones in the circulatory system [5], [25], [26], [49].

Finally, normalizing glucose levels can eradicate the long–term adverse effects of diabetes that affect many patients after decades of disease.

VII. Conclusion

In summary, a low–order nonlinear bihormonal–glucose model accounting for intraperitoneal insulin and glucagon infusions is introduced in this work. The innovations of the model are the use of power–law kinetics for representing intraperitoneal insulin absorption and a separate glucagon sensitivity state. The model was reduced addressing its practical and structural lack of parameter identifiability, given glucose estimations from animal experiments. The parameters of the reduced model were found to exhibit local practical as well as structural identifiability. Both the complete and the reduced model can fit data from animal experiments, where insulin and glucagon boluses were introduced in the IP cavity, which is completely novel to the best of the knowledge of the authors.

Ethical approval

The animal experiments were approved by the Norwegian Food Safety Authority (FOTS number 12948) and were in accordance with “The Norwegian Regulation on Animal Experimentation” and “Directive 2010/63/EU on the protection of animals used for scientific purposes”.

Acknowledgment

The conceptualization of the models and numerical simulations were done by Dr. C. Lopez-Zazueta. Prof. Ø. Stavdahl, Dr. A. L. Fougner, and Dr. C. Lopez-Zazueta contributed to the discussion about the models and the parameter identification analysis. Prof. S. M. Carlsen, Dr. S. C. Christiansen, Dr. M. K. Åm, Dr. A. L. Fougner, Mr. P. Bösch, and Dr. C. Lopez-Zazueta contributed in the discussion of the protocol for the experiments. The experiments were performed by Dr. M. K. Åm, Mr. P. Bösch, and Mrs. O. Lyng. Dr. M. K. Åm collected the data of the experiments with insulin and glucagon intraperitoneal boluses.

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