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IFAC PapersOnLine 52-26 (2019) 219–224

Simple Nonlinear Models for Glucose-Insulin Dynamics: Application to Intraperitoneal Insulin Infusion ⋆

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Abstract:
The design of a model-based control method for an Artificial Pancreas requires a relatively simple and identifiable mathematical model to control glucose levels through hormone delivery. In this work we introduce new, simple nonlinear models to simulate data from experiments where insulin boluses are administrated in the peritoneal cavity. The models account for the delay between insulin administration and its nonlinear transport to other compartments. They were calibrated using experimental data from pigs. The results show that the suggested models are able to describe the data well, with average BIC value of 145. Moreover, the new models were compared with a common linear model which was not able to describe the data well, with BIC value of 920. They were also compared with a common nonlinear model which failed to represent insulin increases in the data and had BIC value of 637. Finally, profile likelihoods were applied for assessing the identifiability of one of the new models.

Keywords: Artificial pancreas, nonlinear models, compartmental systems, power-law kinetics, parameter estimation, identifiability, profile likelihood.

INTRODUCTION

An Artificial Pancreas (AP) system must control the blood glucose level by administrating insulin doses. This can be done using model-based control, but the choice of control model and identification procedure is challenging, since glucose-insulin dynamics are nonlinear and they typically vary between subjects and also over time in each subject [Bianchi et al. (2019); Toffanin et al. (2019)].

Several models have been proposed to simulate the nonlinear dynamics of blood glucose. Some of them are not used for control purposes due to their mathematical complexity and lack of practical identifiability, e.g. Cobelli's model [Cobelli et al. (1982)], the UVA/Padova model [Dalla Man et al. (2014)], etc. Moreover, using large complex models does not assure better performance in closed-loop systems [Bianchi et al. (2019)].

On the other hand, simple linear models cannot represent the nonlinear time-varying dynamics of glucose and insulin. Also, linear models describing insulin-dependent glucose removal in principle allow for negative concentrations [Farina and Rinaldi (2011)], which does not reflect physical reality. Moreover, models without compartments, as the two dimensional Ackerman's linear model [Yipintsoi et al. (1973)], cannot account for the delay between insulin administration and its transport to the circulatory system (blood), which is crucial for subcutaneous or intraperitoneal (IP) insulin infusions.

Candas and Radziuk (1994) proposed a simple nonlinear model (an extension of Bergman's minimal model [Bergman et al. (1979)]) to design a plasma glucose controller. For this simple model they consider insulin compartments and that insulin-dependent glucose removal is proportional to plasma glucose concentration, obtaining in this way a positive nonlinear system. This model was designed for intravenous insulin infusions and an extension for subcutaneous infusions was presented as well. But none of them can account for nonlinear transport between insulin compartments, which might be necessary to appropriately represent IP insulin infusions.

In this work, we propose two simple nonlinear models for glucose-insulin dynamics. These are based on Ackerman's linear model [Yipintsoi et al. (1973)] and Candas and Radziuk model [Candas and Radziuk (1994)], but novel features were added to better represent nonlinear dynamics and experimental data from IP insulin administrations. Our approach proposes using compartments to represent the delay associated with transport of insulin administered

⋆ This work was carried out during the tenure of an ERCIM 'Alain Bensoussan' Fellowship Programme.
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.

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10.1016/j.ifacol.2019.12.261

in the IP cavity to the circulatory system. Moreover, we use power-law kinetics [Crampin et al. (2004); Voit et al. (2015)] to account for nonlinear transport of insulin between two compartments. The use of power-law allows for modeling of a wide range of kinetics assuming that chemical reactions rates can be represented with products of variables raised to non-integer powers.

In Section 1, we present a modified version of Ackerman's linear model [Yipintsoi et al. (1973)] that accounts for insulin compartments and power-law kinetics for insulin transport rates. However, this model is not yet positive.

In Section 2, a nonlinear positive system is introduced. This model was obtained from adapting the model of-Candas and Radziuk (1994) to account for intraperitoneal insulin infusions. Power-law kinetics were used as well to describe nonlinear insulin transport rates.

The two new models were calibrated using data from experiments with pigs, where insulin boluses were administrated in the IP cavity [Dirnena-Fusini et al. (2019)]. Data collection and the parameter estimation technique used are reported in Section 3. The results obtained after the calibration are presented in Section 4.

Ackerman's linear model and the model of Candas and Radziuk were also calibrated using the experimental data, but the results show that these models cannot represent delays and/or nonlinear transport of insulin (see Appendices A and B). Furthermore, the new models fit data with BIC (Bayesian Information Criterion) values lower than those of Ackerman's linear model and Candas and Radziuk model.

In Section 5, parameter profile likelihoods for the model introduced in Section 2 were carried out. The results show that, from a set of 9 parameters, 8 are identifiable and only 1 is practically non-identifiable. Finally, in Section 6 we discuss and give some conclusions about the new approach here presented.

1. A NONLINEAR COMPARTMENTAL MODIFICATION OF ACKERMAN'S MODEL

In this section we propose a simple nonlinear model for simulating glucose-insulin dynamics. The model was inspired by Ackerman's linear model [Yipintsoi et al. (1973)], to which we add two important features. The first one is the delayed transport of insulin from the IP cavity to the circulatory system. The second one is the nonlinear transport of insulin between compartments.

Ackerman's linear model has been used to model blood glucose and plasma insulin responses during slow intravenous infusions of insulin [Yipintsoi et al. (1973)]. But intravenous injections of insulin provides more rapid increase in plasma insulin concentration, compared to intraperitoneal and subcutaneous infusions [Schade et al. (1979)]. As a consequence, Ackerman's linear model cannot represent the delay for the increase in blood insulin levels when infusions are made in the IP cavity (see Figure A.1).

In order to represent delayed transport of insulin, we consider that insulin goes through three different compartments: 1) the IP cavity, 2) an intermediate compartment (IC) between the IP cavity and the circulatory system, and 3) the blood circulatory system (CS). The intermediate compartment can be interpreted as the insulin released from the IP cavity that will be absorbed by the capillaries to go to the circulatory system. Other analogous intraperitoneal insulin absorption kinetics can be considered, e.g. assuming different compartments within the IP cavity as in Matsuo et al. (2003).

Moreover, there is evidence from data [Dirnena-Fusini et al. (2019)] that the transport rate of insulin from the IP cavity to CS might be nonlinear and dependent on insulin doses. In this work, this nonlinearity has been represented using the power-law for reaction kinetics [Crampin et al. (2004); Voit et al. (2015)].

Therefore, we propose the following modified version of Ackerman's model:

$$\begin{aligned}\frac{dG}{dt} &= -m_1 \cdot G(t) - m_2 \cdot I(t) + j \cdot J(t) \\ \frac{dI}{dt} &= -m_3 \cdot I(t) + m_4 \cdot G(t) + m_5 \cdot [i_1(t)]^p \\ \frac{di_1}{dt} &= -m_6 \cdot i_1(t) + m_7 \cdot i_2(t) \\ \frac{di_2}{dt} &= -m_8 \cdot i_2(t) + k \cdot K(t),\end{aligned} \tag{1}$$

where G denotes blood glucose concentration, I blood insulin concentration in CS compartment (minus a basal value), i_1 and i_2 are insulin transport rates from the IC compartment and the IP cavity, respectively. $J(t)$ and $K(t)$ are nonnegative functions representing the rate of exogenous glucose infusion and insulin bolus input, respectively. m_i, j and k are positive parameters depending on the individual, and p is a real number characteristic of the individual as well. Notice that in type 1 diabetes cases, the parameter m_4 can be set to 0, since there is not endogenous insulin production in response to increased glucose levels [Yipintsoi et al. (1973)].

The modified Ackerman's model (1) here proposed represents accurately the data obtained from experiments with pigs, where insulin boluses were administrated in the IP cavity (see Figure 1 and Table 1).

However, system (1), as well as Ackerman's linear model, is not a positive system [Farina and Rinaldi (2011)]. Then, parameters to fit data must satisfy that variables do not attain negative values. This constraint is omitted with the model proposed in the following section, which is a positive nonlinear model.

2. A SIMPLE NONLINEAR POSITIVE MODEL WITH POWER-LAW KINETICS

In Candas and Radziuk (1994) a nonlinear model used for designing a plasma glucose controller is presented. This model already proposes to consider insulin compartments. However, it was used for glycemic control using intravenous and subcutaneous injections of insulin. To adapt the model to intraperitoneal insulin boluses, the insulin input $K(t)$ has to be set in the appropriate compartment. Thus, we consider insulin compartments as in Section 1 and that the insulin input is located in the IP cavity compartment.

Assuming that insulin-dependent glucose removal is proportional to glucose concentration, Candas and Radziuk obtained a system that is nonlinear and positive. However, the model does not allow to represent nonlinear transport between insulin compartments. As in the preceding Section 1, we have used power-law kinetics to represent nonlinear transport of insulin.

We define the following model, based on the model of Candas and Radziuk (1994), to represent data of intraperitoneal insulin administration:

$$\begin{aligned}\frac{dG}{dt} &= -[k_0 + k_1 \cdot I(t)] \cdot G(t) + j \cdot J(t) \qquad (2)\\ \frac{dI}{dt} &= -a_1 \cdot I(t) + a_2 \cdot [i_1(t)]^p\\ \frac{di_1}{dt} &= -a_3 \cdot i_1(t) + a_4 \cdot I(t) + a_6 \cdot i_2(t)\\ \frac{di_2}{dt} &= -a_6 \cdot i_2(t) + a_5 \cdot i_1(t) + k \cdot K(t),\end{aligned}$$

where G is the blood glucose concentration, I the blood insulin concentration in CS compartment (minus a basal value), i_1 and i_2 are insulin transport rates from the IC compartment and the IP cavity, respectively. $J(t)$ and $K(t)$ are nonnegative functions representing the rate of exogenous glucose infusion and insulin administrated in the IP cavity, respectively. a_i, j, k, k_0 and k_1 are positive parameters depending on the individual, and p is a real number depending on the individual as well.

Note 1. Bergman's minimal model adapted for type 1 diabetes is similar to the model presented in Candas and Radziuk (1994), but it accounts for less insulin compartments [Bergman et al. (1979); Chee and Fernando (2007)]

3. DATA COLLECTION AND METHODS

Systems (1) and (2) were calibrated using data from experiments with pigs [Dirnena-Fusini et al. (2019)]. Each experiment was carried out in about 8 hours. Blood glucose levels were measured at least every 5 minutes from intravenous blood samples. Glucose was intravenously infused at constant rate (8 g/h) during all the experiment, except for Pig 1 in which glucose infusion was readjusted based on blood glucose samples analyzed during the experiment (mean rate 7.72 g/h).

Insulin boluses were introduced in the IP cavity. Insulin and porcine insulin were measured from intravenous blood samples. Porcine insulin and glucagon endogenous production were neglected for modeling, since they were suppressed by a combination of octreotide and pasireotide during the experiments [Dirnena-Fusini et al. (2019)].

Insulin levels were measured with ELISA kits (Mercodia, Sweden). For the insulin analysis kit used, 6 mU/L is equivalent to 1 pmol/L.

Note 2. An analysis of a larger data set of these experiments is going to be published later on.

Parameter estimation for each model was carried out using the Nelder-Mead algorithm to minimize the sum of squared errors between the model and data. The *fminsearch* tool was used in Scilab (www.scilab.org) to obtain a minimum of the cost function

$$F(\theta) = \sum_{t \in T_G} [BGA(t) - G(t,\theta)]^2 + \sum_{t \in T_I} [IM(t) - I(t,\theta)]^2,$$

where θ is the vector of parameters to be estimated, $BGA(t)$ and $IM(t)$ represent the data of blood glucose analysis and insulin measured, respectively, T_G and T_I are the time sets at which glucose and insulin were measured, respectively, and $G(t,\theta)$ and $I(t,\theta)$ are state variables of the model with the parameters in θ.

In order to compare the accuracy of the models after parameter estimation, we compute the BIC (Bayesian Information Criterion) values [Burnham and Anderson (2004)] for each model.

4. RESULTS

After parameter estimation, the new models (1) and (2) here proposed gave sound results to approximate glucose-insulin dynamics (see Figures 1-2 and Tables 1-2). Both models efficiently represent the delayed and nonlinear transport of insulin from the IP cavity to the blood circulatory system.

For the parameter sets obtained using experimental data (see method in Section 3), the average BIC values of systems (1) and (2) are 147.21 and 143.18, respectively.

Ackerman's linear model [Yipintsoi et al. (1973)] and the model proposed in Candas and Radziuk (1994) were also calibrated using data from Pig 1 (see Appendices A and B). However, their approximations of data are less accurate than those obtained with the new models (1) and (2) (see Figures A.1-B.1 and Tables A.1-B.1).

The BIC values of Ackerman's linear model and the model of Candas and Radziuk are 919.58 and 631.16, respectively. In conclusion, we obtained that BIC values of the new models (1) and (2) are significantly lower than those of Ackerman's linear model and the model of Candas and Radziuck

Note 3. In Figures 1,2, A.1 and B.1, the values for Insulin IC and Insulin IP rates are normalized with respect to Insulin CS state values.

Table 1. Parameters estimated for system (1) and BIC values for each subject (see Figure 1). Parameter m_4 representing endogenous insulin production was assumed to be zero

Parameter	Pig1	Pig 2	Pig 3	Units
m_1	4.21	14.69	26.13	1/d
m_2	2.67	8.43	23.18	mol/(d.U)
m_3	49.51	36.99	4.66	1/d
m_5	0.16	0.0017	0.0098	mU/(L.d^{1-p})
m_6	173.06	659.87	69.15	1/d
m_7	290.35	460.30	106.84	1/d
m_8	237.66	119.95	115.50	1/d
j	0.86	2.13	6.00	h.mol/(d.L^2)
k	13329	23123	16319	1/(U.d^2)
p	2.25	2.71	1.95	-
BIC	209.62	49.26	182.74	

5. PARAMETER IDENTIFICATION

Although systems (1) and (2) give similar approximations of the data, system (2) has lower BIC values in average.

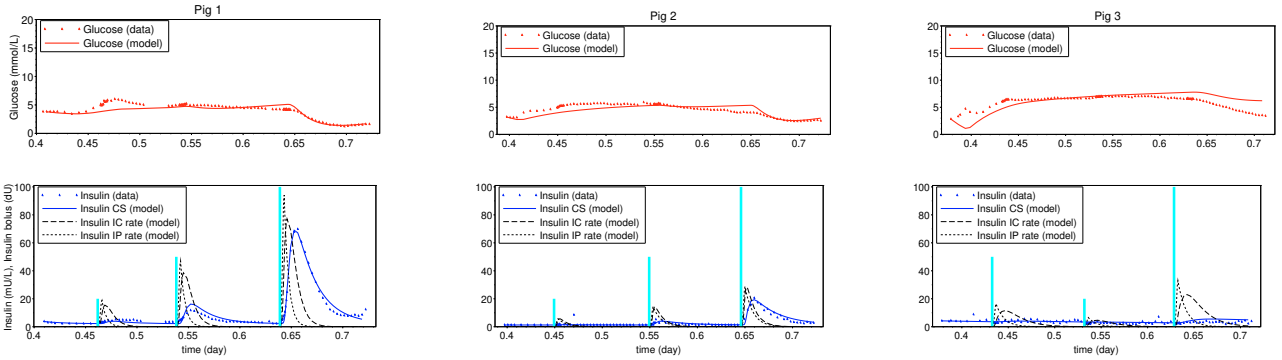

Fig. 1. Numerical solution of the nonlinear compartmental system (1) compared to experimental data. The parameters estimated for system (1) are described in Table 1.

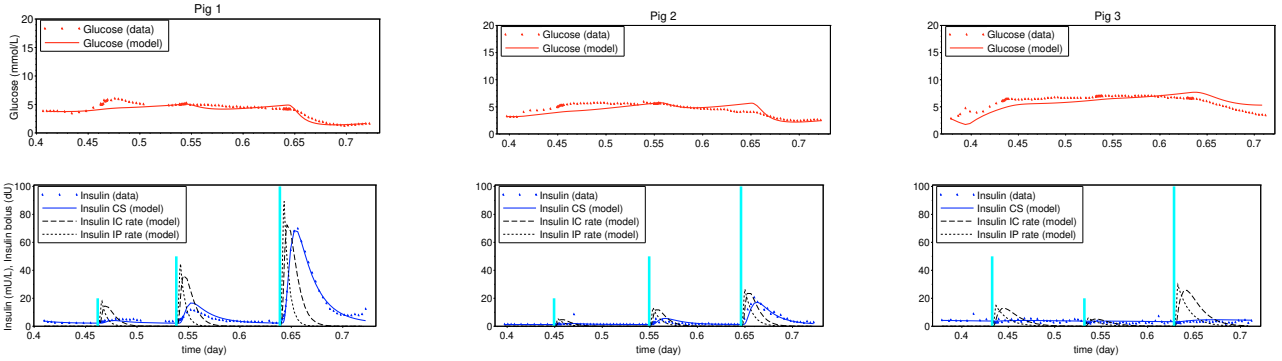

Fig. 2. Numerical solution of the positive nonlinear system (2) compared to experimental data. The parameters estimated for system (2) are described in Table 2.

Table 2. Parameters estimated for system (2) and BIC values for each subject (see Figure 2). Parameters a_4 and a_5 (representing reverse transport between insulin compartments) were assumed to be negligible, thus equal to zero.

Parameter	Pig 1	Pig 2	Pig 3	Units
a_1	56.00	60.00	3.50	1/d
a_2	0.62	1.30	0.55	mU/(L.d^{1-p})
a_3	163.00	223	131.00	1/d
a_6	221.00	131.00	79.00	1/d
k_0	0.0001	0.01	0.50	L/(d.mU)
k_1	0.94	3.00	11.50	L/(d.mU)
j	0.40	0.50	4.50	h.mol/(d.L^2)
k	9980	10000	10100	1/(U.d^2)
p	2.20	1.87	1.22	-
BIC	210.30	85.93	133.30	

Furthermore, system (2) is positive, while system (1) could attain negative values if its set of parameters is not selected accurately and when blood insulin levels, represented by the $I(t)$ state, are sufficiently large.

For these reasons, system (2) was selected as the best model and profile likelihoods [Kreutz et al. (2013)] for its parameters were computed. The results are presented in Figure 3. All the parameters, except for k_0, have finite confidence intervals under the confidence thresholds, leading to conclude that they are identifiable.

The only practically non-identifiable parameter detected is k_0, which represents removal of glucose that is independent of insulin. Since the profile likelihood of k_0 flattens towards small values, we can only conclude that k_0 should have a small value (in the context of these experiments).

6. DISCUSSION AND CONCLUSIONS

In this paper we have presented the simple nonlinear models (1) and (2) to simulate glucose-insulin dynamics. The models are able to represent data from experiments with intraperitoneal insulin boluses. This was achieved considering different insulin compartments and power-law kinetics.

In the models proposed here, we have considered power-law kinetics for the transport of insulin to the circulatory system, when insulin is administrated in the IP cavity. The use of power-law kinetics for modeling insulin nonlinear dynamics has been introduced in this work. In general, previously published models used nonlinear dynamics to describe glucose utilization [Bergman et al. (1979); Candas and Radziuk (1994); Dalla Man et al. (2014)] or insulin synthesis and secretion controlled by blood glucose levels (non-diabetic case) [Cobelli et al. (1982)].

The nonlinear dynamical behavior of insulin described in this paper has not been considered before, probably due to lack of insulin concentration data after using more than one insulin bolus during the same experiment (e.g. [Cobelli

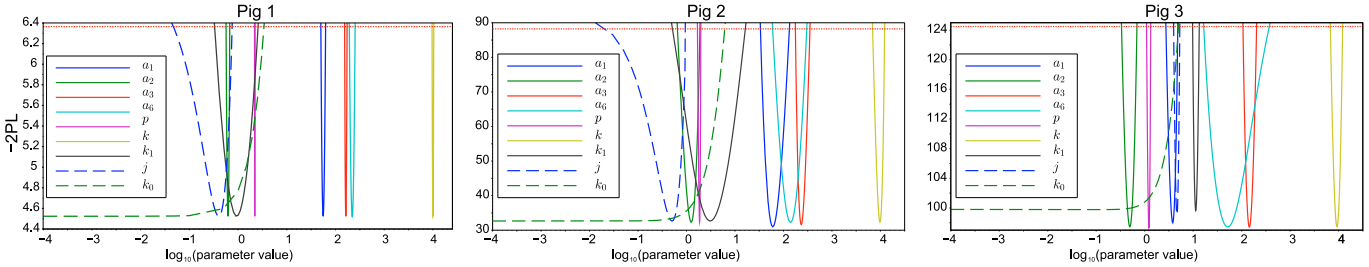

Fig. 3. Parameter Profile Likelihood (PL) for system (2) and Pigs 1-3. Red dotted horizontal lines denote the confidence thresholds with 99% confidence. For these experiments, parameter k_0 (the rate of insulin-independent glucose uptake) is practically non-identifiable and its profile flattens towards low values. The rest of the parameters are identifiable in their respective finite confidence intervals.

et al. (1982); Candas and Radziuk (1994); Matsuo et al. (2003); Magdelaine et al. (2015)]) and in particular for intraperitoneal insulin infusions.

The practical identifiability of one of the new models has been observed. Computing profile likelihoods has shown that, out of a set of 9 parameters, 8 parameters are identifiable.

The only practically non-identifiable parameter corresponds to the insulin-independent consumption of glucose. However, this practical non-identifiability might be due to the experiments conditions (e.g. constant glucose infusions and short fasting states). It is well known that there exists glucose uptake independent of insulin which, for instance, maintains the supply of glucose for the brain, the central nervous system and red blood cells [Chee and Fernando (2007)]. We suggest to keep this parameter representing insulin-independent glucose uptake in the model, since it can be useful in other scenarios where this effect is more dominant. For the case of these short-lasting animal experiments, this parameter just needs to be small or zero and is practically negligible.

Future work is to consider larger glucose-dynamics models where the transport of hormones between compartments is delayed and nonlinear, as it has been presented in this work.

Appendix A. ACKERMAN'S LINEAR MODEL

Ackerman's model [Yipintsoi et al. (1973)] accounts for the equations of blood glucose and hormone concentrations:

$$\begin{aligned}\frac{dG}{dt} &= -m_1 \cdot G(t) - m_2 \cdot I(t) + j \cdot J(t) \qquad \text{(A.1)}\\ \frac{dI}{dt} &= -m_3 \cdot I(t) + m_4 \cdot G(t) + k \cdot K(t),\end{aligned}$$

where G represents blood glucose, I is the effective hormone level in blood (minus a basal level), m_1, m_2, m_3 and m_4 are constants characteristic of the individual, J and K are the rates of exogenous infusions of glucose and hormone, respectively.

Model (A.1) fails to represent delayed and nonlinear transport of insulin from the IP cavity to the circulatory system (see Figure A.1) .

Appendix B. CANDAS AND RADZIUK MODEL

To adapt model proposed in Candas and Radziuk (1994) to the case where insulin is administrated in the IP cavity,

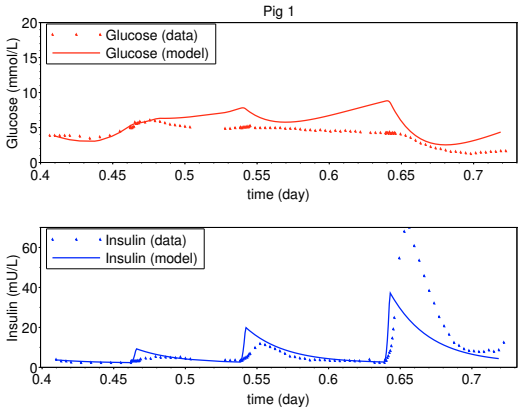

Fig. A.1. Ackerman's linear model (A.1) compared to experimental data. The estimated parameters are described in Table A.1.

Table A.1. Parameters estimated for Ackerman's linear model (A.1).

Parameter	Pig 1	Units
m_1	9.72	1/d
m_2	13.39	(mol/d.U)
m_3	36.34	1/d
m_4	0.00032	(U/d.mol)
j	3.60	(h.mol/d.L^2)
k	1758	1/(d.kL)
BIC	919.58	

we consider the peripheral compartment i_2 as the IP cavity and that insulin-dependent glucose removal $I(t)$ is proportional to blood insulin concentration (minus a basal value). Thus, we write

$$\begin{aligned}\frac{dG}{dt} &= -[k_0 + k_1 \cdot I(t)] \cdot G(t) + j \cdot J(t) \qquad \text{(B.1)}\\ \frac{dI}{dt} &= -a_1 \cdot I(t) + a_2 \cdot i_1(t)\\ \frac{di_1}{dt} &= -a_3 \cdot i_1(t) + a_4 \cdot I(t) + a_6 \cdot i_2(t)\\ \frac{di_2}{dt} &= -a_6 \cdot i_2(t) + a_5 \cdot i_1(t) + k \cdot K(t)\end{aligned}$$

where G and I are glucose and insulin blood concentrations, respectively, i_1 and i_2 are insulin transport rates, a_i, k_0, k_1, j and k are nonnegative parameters, $J(t)$ and $K(t)$ are glucose and insulin systemic appearance, respectively.

Notice that kinetics of system (B.1) are nonlinear only for the equation corresponding to blood glucose concentra-

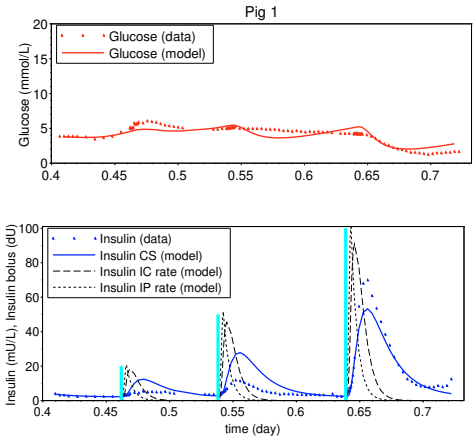

Fig. B.1. Candas and Radziuk model (B.1) compared to experimental data. The estimated parameters are described in Table B.1.

tion. Therefore, this model cannot represent the nonlinear relation between insulin bolus administration and the increase of insulin concentration in blood (see Figure B.1).

Table B.1. Parameters estimated for Candas and Radziuk model (B.1).

Parameter	Pig 1	Units
a_1	55.83	1/d
a_2	81.82	mU/L
a_3	232.10	1/d
a_4	0.0035	L/(mU.d^2)
a_5	1.75	1/d
a_6	207.54	1/d
k_0	1.0037	L/(d.mU)
k_1	1.083	L/(d.mU)
j	1.025	h.mol/(d.L^2)
k	12654	1/(U.d^2)
BIC	637.00	

ACKNOWLEDGEMENTS

Animal trials and data collection were performed by Ilze Dirnena-Fusini, Marte Kierulf Åm, Patrick Bösch and Oddveig Lyng.

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

The experiments were conducted at the Comparative Medicine Core Facility (CoMed), Norwegian University of Science and Technology (NTNU). CoMed is funded by the Faculty of Medicine at NTNU and Central Norway Regional Health Authority.

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