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# A rat–human scale-up procedure for the endocrine system

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ABSTRACT

The main contribution of this work is to present a detailed scale-up procedure between human and rats models to more accurately predict what would happen in human beings, based on the experimental results obtained from rats. This procedure begins using the human model, given by Sorensen (1985). The proposed scale-up technique required to establish some assumptions, to do an intensive search in the literature about organs volumes and flow rates of body rats and a dedicated experimental work in the laboratory with these animals. Even though it is mainly focused on studying the endocrine system behavior to obtain a proper in in silico healthy rat it can be extended to study another body regions. Several simulation results with the obtained rat model are included and confronted with experimental data of ten healthy rats. The analogy between human and rat dynamic behavior after equivalent meal intakes are also discussed.



## 1. Introduction

During the last three decades, the research community has made important efforts to develop different mathematical models to represent the glucose-insulin interaction in healthy and diabetic humans. Particularly, in 2008 the US Food and Drug Administration approved a type I diabetic patient simulator as a substitute to animal trials in the pre-clinical testing of closed-loop control algorithms Kovatchev et al. (2009) to formulate the basis for an artificial pancreas. Even though, it is highly recommended that human clinical tests were preceded by at least one preclinical trial on laboratory animals providing substantial evidence of efficacy.

As a common research methodology in this area, several pretests are done in rats making it possible to infer the real effects in human beings. In recent years, a very detailed and complex computer model (cell level) of the progression of type 1 diabetes in the NOD mouse (Type 1 Diabetes PhysioLab (Burn, 2010)) has been developed but it is only commercially available. Therefore, a first approach was presented in Campetelli et al. (2010), where the mathematical model of the glucose-insulin system developed by Kovatchev et al. (2009) for humans was adjusted to diabetic rats. In that work the main purpose was to get insight into accurate scaling factors between humans and rats. Even though the obtained results were promising, it was difficult to do a scale-up because the model of Kovatchev et al. (2009) does not involve geometrical relationships. For this reason, we considered the first-principles model of Sorensen (1985) because it is the only physiologically based compartmental model which takes into account different parts of the human body such as brain, heart, lungs, liver, gut, kidneys and periphery. Hence, it represents a good starting point to test the scaling procedure recommended in Hall et al. (2012) and gives the possibility of being extended to larger problems.

So, based on the preliminary results presented at Campetelli et al. (2013), in this paper the endocrine system model for healthy subjects of Sorensen (1985) is scaled for its use with healthy rats. The calculations done here are based on data obtained from a thorough search involving blood flow rates, organs volume and weight of rats together with some useful considerations reported in the literature and others based on practical experience. The predictions of this scaled model of rats are confronted with experimental data obtained in our laboratory. This allowed us to quantify the potentiality of our methodology and to check if the scale-up is able to

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**Nomenclature**

*Dalla Man meal intake model variables*
$d$ (mg) amount of ingested glucose
$Q_{sto1}$ (mg) amount of glucose in the stomach in the solid phase
$Q_{sto2}$ (mg) amount of glucose in the stomach in the liquid phase
$Q_{sto}$ (mg) total amount of glucose in the stomach
$Q_{gut}$ (mg) glucose mass in the intestine
$\Gamma_{meal}$ (mg/min) glucose rate of appearance in plasma

*Parameters*
$k_{gri}$ ($\text{min}^{-1}$) rate of grinding
$k_{empt}$ ($\text{min}^{-1}$) rate constant of gastric emptying
$k_{abs}$ ($\text{min}^{-1}$) rate constant of intestinal absorption $f$ fraction of intestinal absorption that actually appears in plasma

*Sorensen model variables*
$A$ auxiliary equation state
$F$ (I: *dimensionless*, N: l/min) fractional clearance
$G$ (mg/dl) glucose concentration
$I$ (mU/l) insulin concentration
$N$ (normalized, *dimensionless*) glucagon concentration
$Q$ (l/min) vascular plasma flow rate
$q$ (dl/min) vascular blood flow rate
$T$ (min) transcapillary diffusion time constant
$V$ (l) volume
$v$ (dl) volume
$\Gamma$ (mg/min or mU/min) metabolic source or sink rate

*Model sub- and superscripts*
$A$ hepatic artery
$B$ brain
$BU$ brain uptake
$C$ capillary space
$G$ glucose
$H$ heart and lungs
$HGP$ hepatic glucose production
$HGU$ hepatic glucose utilization
$I$ insulin
$IHGP$ insulin effect on $HGP$
$IHGU$ insulin effect on $HGU$
$K$ kidney
$KC$ kidney clearance
$KE$ kidney excretion
$L$ liver
$LC$ liver clearance
$N$ glucagon
$NHGP$ glucagon effect on $HGP$
$P$ periphery (muscle/adipose tissue)
$PC$ peripheral clearance
$PGU$ peripheral glucose uptake
$PIR$ pancreatic insulin release
$PNC$ pancreatic glucagon clearance
$PNR$ pancreatic glucagon release (normalized)
$RBCU$ red blood cell uptake
$S$ gut (stomach/intestine)
$SU$ gut uptake
$T$ tissue space

*Model first superscripts*
$G$ glucose
$I$ insulin
$r$ g1ucagon
$B$ basal value
$N$ normalized value (divided by basal value)

*Insulin secretion model variables*
$P$ (*dimensionless*) potentiator
$I$ (*dimensionless*) inhibitor
$Q$ (Humans: U, Rats: μg) labile insulin
$S$ (U/min) insulin secretion rate
$X$ (*dimensionless*) nonlinear effect of glucose on early insulin release
$Y$ (*dimensionless*) secretory effect of glucose
$P_\infty$ (*dimensionless*) nonlinear effect of glucose on late insulin release

*Parameters*
$\alpha$, $\beta$ ($\text{min}^{-1}$) inverse time constants
$K$ ($\text{min}^{-1}$) rate constant
$M_1$, $M_2$, (*dimensionless*) constants
$\gamma$ (Humans: U/min, Rats: μ g/min) rate constant
$Q_0$ (Humans: U, Rats: μg) quantity of labile insulin for $G_H^C = 0$
$\delta$ (*dimensionless*) constant
$G_0$ (mg/dl) the value of $G_H^C$ for which $X = 1/2$
$X_{01}$, $X_{02}$, $X_{03}$ (*dimensionless*) constants

*Other symbols*
$V_{Ci}$, $V_{Cj}$ (l) capillary blood volume of organs $i$, $j$
$M_i$, $M_j$ (kg) masses of organs $i$, $j$
$Q_{Bi}$, $Q_{Bj}$ (l/min) blood flow rates to organs $i$, $j$
$V_{total}$, $V_{capillary}$, $V_{interstitial}$, $V_{intracellular}$ (l) volumes
$VO_2$ (ml/kg/min) oxygen consumption rate
$CHO_{human}$, $CHO_{rat}$ (g) carbohydrate content of ingested meal

predict well the real impact on human beings observed through the experiments with rats. Therefore, accurate models for rats together with a confident scaling procedure will be of help to speed up the knowledge gain from experimental trials and to address safety concerns.

## 2. The endocrine system model framework and scale-up methodology

In this section a summary of the model of Sorensen (1985) will be given, together with a description of the scale-up method applied to estimate the parameters. The original equations of the mathematical model given by Sorensen (1985) are detailed in Appendix A.

The simulator developed by Sorensen (1985) is a first principles model which has a physiological structure. It was obtained from experimental evidence to formulate and validate metabolic processes of the compartmental model on the whole organ and tissue level, including glucagon as a counter-regulatory hormone. The glucose-insulin model is governed by 22 nonlinear ordinary differential equations and it is divided into three subsystems: glucose, insulin and glucagon. The first two subsystems were modeled for the brain, arterial system (heart and lungs), liver, gut (stomach and intestines), kidney, and periphery (muscle and adipose tissue) compartments. The glucagon was modeled as a single blood pool compartment. However, due to some typographical errors and inconsistencies in the differential equations found at the work of

**Table 1**
Total blood volume distribution in the rat of 277 g.

| | % Blood volume | Volume (l) |
|---|---|---|
| Capillaries, arterioles, and venules | 10 | $2.07E^{-3}$ |
| Heart, lungs, and arteries | 30 | $6.21E^{-3}$ |
| Veins | 60 | $1.24E^{-2}$ |
| Total | 100 | $2.07E^{-2}$ |

Sorensen (1985) and reported by Parker et al. (2000), Colmegna and Sánchez Pe na (2012), in this work the corrections done by Colmegna and Sánchez Pe na (2012) were taken into account.

In addition, the Sorensen's model was extended by integrating the model of Dalla Man et al. (2006) for considering the rate of glucose appearance in blood ($\Gamma_{meal}$). It was chosen because it has a more detailed representation of glucose transit through the gastrointestinal tract and the corresponding equations are included too in Appendix A. Hence, the scale-up procedure proposed here assumes the same glucose rate of appearance of humans and rats.

To understand the methodology used to obtain a scaled model of the rat, step by step, the same procedure given by Sorensen (1985) is followed but using specific data for the rats. In addition, the parameters of the model are classified into two groups; the first one corresponds to the physical parameters such as blood flow rates and volume of compartments. The second group involves the parameters of the metabolic rate functions which model the effects of the metabolic reactions occurring in the different organs considered in the physiological model.

### 2.1. Physical parameters

The model of Sorensen considers a healthy subject of 70 kg which was adopted as an average person. Here, a rat of 277 g of body weight is considered as an average animal, so the calculations done to show the scale-up procedure are based on this weight. Then, a total blood volume of about $2.07E^{-2}$ l, corresponds to that weight (277 g) which is assumed to be distributed as it is shown in Table 1, in accordance to the distribution given by Sorensen for humans.

The total capillaries (plus venule and arterioles) blood volume is $2.07E^{-3}$ l and this was distributed among the tissue regions assuming that the ratio of capillary blood volume between the ith and jth organs is given by Bischoff and Brown (1966):

$$\frac{V_{Ci}}{V_{Cj}} = \left(\frac{M_i}{M_j}\right)^{1/3} \left(\frac{Q_{Bi}}{Q_{Bj}}\right) \tag{1}$$

where $V_C$ is capillary blood volume and $M$ and $Q_B$ represent organ mass and blood flow rate, respectively. Eq. (1) was based on the postulate that capillary flow rates are about the same in every body region and that the average capillary length is related to the total size of the region (Bischoff and Brown, 1966). Capillary blood volumes calculated in this manner are presented in Table 2.

To reduce computational costs, capillary blood volumes were not directly employed in modeling. Regional blood volumes were represented in terms of blood equilibration volumes instead (Table 2). At any given time, the majority of blood is contained in the venous vessels (see Table 1). For modeling, it was assumed that a certain fraction of the venous pool is essentially in equilibrium with the capillary blood of the region from which it flows. Thus, venous equilibration volumes were computed by distributing the total venous volume among the body regions on the basis of their respective fractional blood flows. Regional blood equilibration volumes were then obtained by summing the respective venous equilibration and capillary blood volumes. These calculations are summarized in Table 2. Blood contained in the arterial vessels was lumped with cardiopulmonary blood volume of $6.21E^{-3}$ l (see Tables 1 and 2).

**Table 3**
Approximate body fluid distribution of a 277 g rat.

| | Volume (l) |
|---|---|
| Extracellular fluid: | $5.82E^{-2}$ |
| Blood plasma | $1.25E^{-2}$ |
| Interstitial-lymph | $3.32E^{-2}$ |
| Dense connective tissue, cartilage | $1.25E^{-2}$ |
| Intracellular fluid: | $9.14E^{-2}$ |
| Blood cells | $8.24E^{-3}$ |
| Extravascular | $8.32E^{-2}$ |
| Total | $1.5E^{-1}$ |

Interstitial and intracellular fluid volumes were estimated using the approximate whole-body fluid distribution volumes shown in Table 3.

The distribution of Edelman and Leibman (1959) was adapted to a 277 g rat in order to build Table 3. For modeling, it was assumed that the ratio of interstitial fluid to cellular fluid volume is the same for all body regions (Bischoff and Brown, 1966). Thus, from Table 3:

$$\frac{V_{interstitial}}{V_{intracellular}} = \frac{3.32E^{-2} + 1.25E^{-2}}{8.32E^{-2}} = 0.55 \tag{2}$$

Using this expression, and noting that for each body region:

$$V_{total} = V_{capillary} + V_{interstitial} + V_{intracellular} \tag{3}$$

where total volume is approximated by equating with total organ or tissue mass, the interstitial and intracellular fluid volumes were approximated for each body region, and these values are given in Table 4.

According to Sorensen (1985), for modeling, the peripheral interstitial fluid volume can be calculated from Eqs. (2) and (3). The organ masses and blood flow rates of rats were taken from the reported data recorded by Hall et al. (2012) which can be seen in Table 4, but blood flow rate of the hepatic artery was taken from Daemen et al. (1989). Then, with this data, it was possible to estimate the interstitial fluid volumes of Table 3 of about $3.32E^{-2}$ l. The final calculation of the physical parameters was done taking into account that the water content of whole blood is roughly 84 volume percent, the blood volumes (Table 2) and flow rates (Table 4) as estimated for a 277 g rat were reduced by 16% for glucose modeling. Moreover, as the average red blood cells content of whole blood is about 40 volume percent, the blood volumes and flow rates as

**Table 2**
Regional distribution of blood volume.

| Organ or tissue | % Blood flow | Venous equilibration volume (l) | Capillary volume (l) | Blood equilibration volume (l) |
|---|---|---|---|---|
| Brain | 4.8 | $6.01E^{-4}$ | $7.79E^{-5}$ | $6.79E^{-4}$ |
| Heart and lungs | | | | $6.21E^{-3}$ |
| Liver | 28.5 | $3.55E^{-3}$ | $4.6E^{-4}$ | $4E^{-3}$ |
| Gut | 18.2 | $2.26E^{-3}$ | $2.19E^{-4}$ | $2.48E^{-3}$ |
| Kidney | 22.3 | $2.77E^{-3}$ | $2.11E^{-4}$ | $2.98E^{-3}$ |
| Periphery | 26.1 | $3.24E^{-3}$ | $1.1E^{-3}$ | $4.34E^{-3}$ |
| Total | 100 | $1.24E^{-2}$ | $2.07E^{-3}$ | $2.07E^{-2}$ |

**Table 4**
Estimated distribution volumes and blood flow rates for an average 277 g rat.

| Organ or tissue | Mass (kg) | Blood flow rate (l/min) | Interstitial fluid volume (l) | Intracellular fluid volume (l) |
|---|---|---|---|---|
| Brain | $1.08E^{-2}$ | $2E^{-3}$ | $3.8E^{-3}$ | $6.92E^{-3}$ |
| Heart and lungs | [a] | $4.13E^{-2}$ | [a] | [a] |
| Liver | $1.08E^{-2}$ | $1.18E^{-2}$ | $3.67E^{-3}$ | $6.68E^{-3}$ |
| Gut | $4.5E^{-3}$ | $7.52E^{-3}$ | $1.52E^{-3}$ | $2.76E^{-3}$ |
| Kidney | $2.2E^{-3}$ | $9.23E^{-3}$ | $7.05E^{-4}$ | $1.28E^{-3}$ |
| Periphery | $1.95E^{-1}$ | $1.08E^{-2}$ | $2.35E^{-2}$ | $6.55E^{-2}$ |
| (Hepatic artery) | | $2.27E^{-3}$ | | |
| Total | $2.23E^{-1}$ | $4.13E^{-2}$ | $3.32E^{-2}$ | $8.32E^{-2}$ |

[a] Tissue (extravascular) spaces of the heart and lungs have been lumped into periphery.

estimated for a 277 g rat (Table 5) were reduced by 40 percent for insulin modeling (Sorensen, 1985). Then, all the resulting vascular parameter values incorporated into the model given at Appendix A are detailed in Table 5.

The total distribution volume for glucagon in the human body was considered by Sorensen (1985) approximately equal to that for insulin. In this work the same assumption is adopted for rats. Thus, summing the vascular and interstitial fluid volumes of the insulin model gives a glucagon distribution volume of $V_N = 0.04566$ l. In compliance with Oshima et al. (1988), the metabolic glucagon clearance rate is $F_{PNC} = 0.018$ l/min.

All the metabolic rates are based on the basal value of the hepatic glucose production rate which is $\Gamma^B_{HGP} = 4$ mg/min. This value was calculated as the average of those reported in the literature presented at Table 6 and multiplied by the rat weight.

Then, this source is distributed to the sinks, maintaining for the rat the same proportions of the human model given at Sorensen (1985) as can be seen in Table 7.

Furthermore, it was assumed that the fractional clearances of insulin by the liver, peripheral tissues and kidney are equal to those for humans ($F_{PC}$, $F_{KC}$ and $F_{LC}$). The same assumption was made for the diffusion time constants of glucagon and insulin for mass transfer ($T^G_P$, $T^I_P$, $T_I$ and $T^I_R$) but for glucose ($T_B$) it was reduced so that the interstitial brain glucose ($G^T_B$) be a positive value. These parameters and the ones related to the insulin secretion model (described at the end of Appendix A) are shown in Table 8. It is worth mentioning that the insulin secretion model was originally developed for healthy rats, so the values of its parameters were not changed. Apart from that, it is only a model of insulin release and not from the whole endocrine system of rats (Landahl and Grodsky, 1982).

**Table 5**
Model parameters.

| Parameter | Units | Rats | Humans |
|---|---|---|---|
| $q_B$ | dl/min | 0.0168 | 5.9 |
| $q_L$ | dl/min | 0.0991 | 12.6 |
| $q_K$ | dl/min | 0.0775 | 10.1 |
| $q_P$ | dl/min | 0.0906 | 15.1 |
| $q_H$ | dl/min | 0.3473 | 43.7 |
| $q_S$ | dl/min | 0.0632 | 10.1 |
| $q_A$ | dl/min | 0.0191 | 2.5 |
| $v^C_B$ | dl | 0.0127 | 3.5 |
| $v^C_H$ | dl | 0.0522 | 13.8 |
| $v^I_B$ | dl | 0.0380 | 4.5 |
| $v^C_S$ | dl | 0.0208 | 11.2 |
| $v^C_L$ | dl | 0.0336 | 25.1 |
| $v^C_K$ | dl | 0.0251 | 6.6 |
| $v^C_P$ | dl | 0.0365 | 10.4 |
| $v^T_P$ | dl | 0.2354 | 67.4 |
| $Q_B$ | l/min | 0.0012 | 0.45 |
| $Q_L$ | l/min | 0.0071 | 0.9 |
| $Q_K$ | l/min | 0.0055 | 0.72 |
| $Q_P$ | l/min | 0.0065 | 1.05 |
| $Q_H$ | l/min | 0.0248 | 3.12 |
| $Q_S$ | l/min | 0.0045 | 0.72 |
| $Q_A$ | l/min | 0.0014 | 0.18 |
| $V^C_B$ | l | 0.0002 | 0.265 |
| $V^C_H$ | l | 0.0037 | 0.985 |
| $V^C_S$ | l | 0.0008 | 0.945 |
| $V^C_L$ | l | 0.0012 | 1.14 |
| $V^C_K$ | l | 0.0002 | 0.505 |
| $V^C_P$ | l | 0.0062 | 0.735 |
| $V^T_P$ | l | 0.0235 | 6.3 |

**Table 6**
Basal hepatic glucose production rate.

| $\Gamma^B_{HGP}$ (mg/kg/min) | NÂ Rats | Author |
|---|---|---|
| 10.6 | 35 | Rossetti et al. (1993) |
| 18.9 | 10 | Rossetti et al. (1993) |
| 12.7 | 16 | Giaccari et al. (1998) |
| 19.5 | 17 | Giaccari et al. (1998) |
| 11.8 | 5 | Gupta et al. (2000) |
| 11.2 | 6 | Gupta et al. (2000) |
| 12.3 | 6 | Gupta et al. (2000) |
| 11.2 | 6 | Gupta et al. (2000) |
| 11.9 | 6 | Gupta et al. (2000) |
| 18.7 | 12 | Li and Yang (2004) |
| 19 | 12 | Li and Yang (2004) |
| 14.3 | | |

## 2.2. Metabolic rate functions parameters

In this section the description of the procedure followed to obtain the second group of parameters is presented. To finally fit the simulations of the model to the experimental data, the knowledge gained by Parker (1999) working with Sorensen's model was exploited. After a sensitivity analysis of the parameters of the model he concluded that the most relevant were those related to the metabolic sources and sinks. He used some of those parameters to create different patients with different dynamics. The proposal here is to take advantage of that to improve the predictions of the scaled rat model. Then, the objective is to test by means of dynamic simulation, the evolution of the adapted rat model confronted with the available experimental data of blood glucose and insulin after a controlled meal intake.

Therefore, the second group of parameters were adjusted using the Parameter Estimation Toolbox of Simulink, Matlab. There are 9

**Table 7**
Summary of basal glucose balance in a 277 g rat.

| | Rate (mg/min) |
|---|---|
| Hepatic glucose production ($\Gamma^B_{HGP}$) | 4 |
| Total glucose uptake | 4 |
| Brain ($\Gamma^B_{BU}$) | 1.8 |
| Peripheral (Muscle and Adipose) ($\Gamma^B_{PGU}$) | 0.9 |
| Liver ($\Gamma^B_{HGU}$) | 0.5 |
| Gut ($\Gamma^B_{SU}$) | 0.5 |
| Red blood cells ($\Gamma^B_{RBCU}$) | 0.3 |

**Table 8**
Model parameters.

| Parameter | Units | Rats | Humans |
|---|---|---|---|
| $V_N$ | l | 0.0457 | 9.93 |
| $F_{PNC}$ | l/min | 0.018 | 0.91 |
| $F_{PC}$ | Dimensionless | 0.15 | 0.15 |
| $F_{KC}$ | Dimensionless | 0.3 | 0.3 |
| $F_{LC}$ | Dimensionless | 0.4 | 0.4 |
| $T_B$ | min | 0.21 | 2.1 |
| $T_P^G$ | min | 5 | 5 |
| $T_P^I$ | min | 20 | 20 |
| $T_I$ | min | 25 | 25 |
| $T_R^I$ | min | 65 | 65 |
| $\Gamma_{BU}^B$ | mg/min | 1.8 | 70 |
| $\Gamma_{RBCU}^B$ | mg/min | 0.3 | 10 |
| $\Gamma_{SU}^B$ | mg/min | 0.5 | 20 |
| $\Gamma_{HGP}^B$ | mg/min | 4 | 155 |
| $\Gamma_{HGU}^B$ | mg/min | 0.5 | 20 |
| $\Gamma_{PGU}^B$ | mg/min | 0.9 | 35 |
| $K$ | $min^{-1}$ | 0.035 | 0.00794 |
| $\alpha_s$ | $min^{-1}$ | 0.05 | 0.0482 |
| $\beta_s$ | $min^{-1}$ | 0.6 | 0.931 |
| $M_1$ | Dimensionless | 0.27 | 0.00747 |
| $M_2$ | Dimensionless | 0.9 | 0.0958 |
| $\gamma$ | μg/min - U/min [a] | 0.45 | 0.575 |
| $Q_0$ | μg - U [a] | 1.2 | 6.33 |
| $\delta$ | Dimensionless | 2 | 1.11 |
| $G_0$ | mg/dl | 150 | 132 |
| $X_{01}$ | Dimensionless | 4 | 3.27 |
| $X_{02}$ | Dimensionless | 4 | 3.02 |
| $X_{03}$ | Dimensionless | 1 | 5.93 |

[a] μg for rats and U for humans.

hyperbolic tangent functions (Appendix A). The rate of kidney glucose excretion ($\Gamma_{KE}$) was assumed equal to that of humans. Each one of the rest of the functions has 4 parameters to be adjusted using a Simplex optimization algorithm under the assumption of presenting analogous behavior to the human subject. The rest of the parameters which were mentioned in Section 2.1 were not changed. The model was adjusted to real measurements of blood glucose concentration and insulin of 10 healthy rats (shown at Table 11).

## 3. The meal intake scale-up

It is a well-known issue the fact that the daily food intake of rats, in relation to their body weight, is larger than the intake of humans. Based on our experience, it was decided to quantify this relationship according to the oxygen consumption ($VO_2$) measurements of humans and rats (3.5 and 52.8 ml/kg/min, respectively) which were presented in a previous work (Fina et al., 2012). As this quantity is proportional to the amount of digested food, the quantity of ingested carbohydrates (assuming that 60% corresponds to glucose), per species, per day (average values) can be calculated by means of different well-known conversion factors like the energy content of oxygen and glucose (Lehninger, 2005), giving as a result 264.6 and 15.8 g/day for humans and rats respectively.

From these quantities the following expression arises:

$$\frac{CHO_{human}}{CHO_{rat}} = \frac{264.6}{15.8} = 16.7 \tag{4}$$

where *CHO* means mass of carbohydrates.

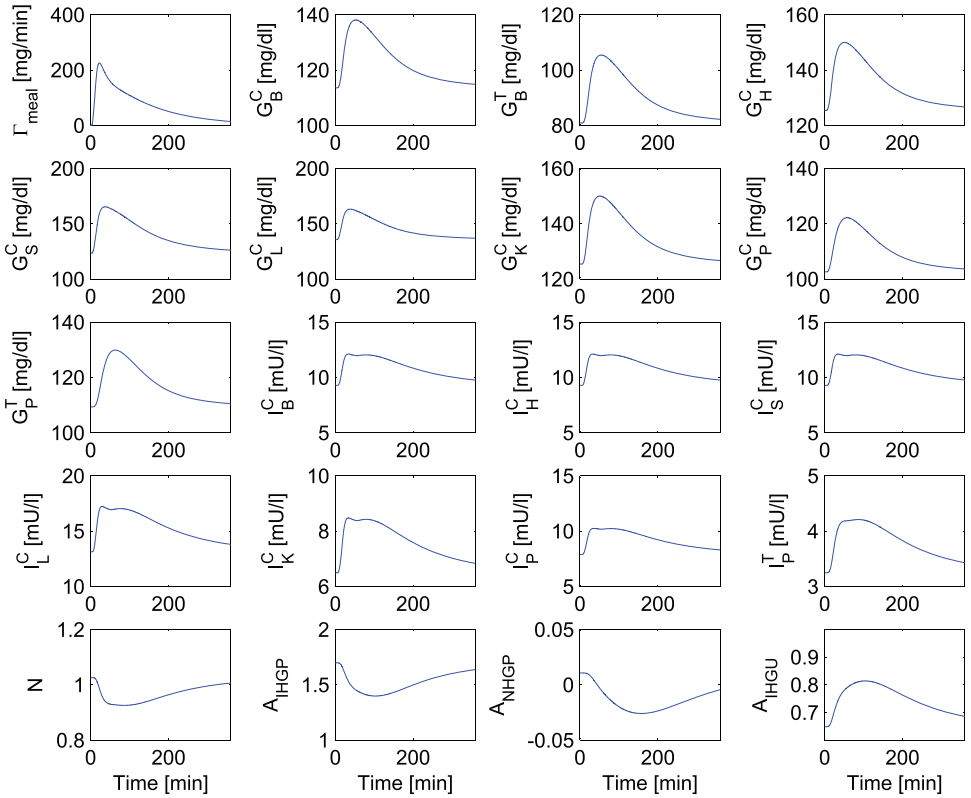


**Fig. 1.** Simulation of Sorensen's normal human after a 31.44 g meal.

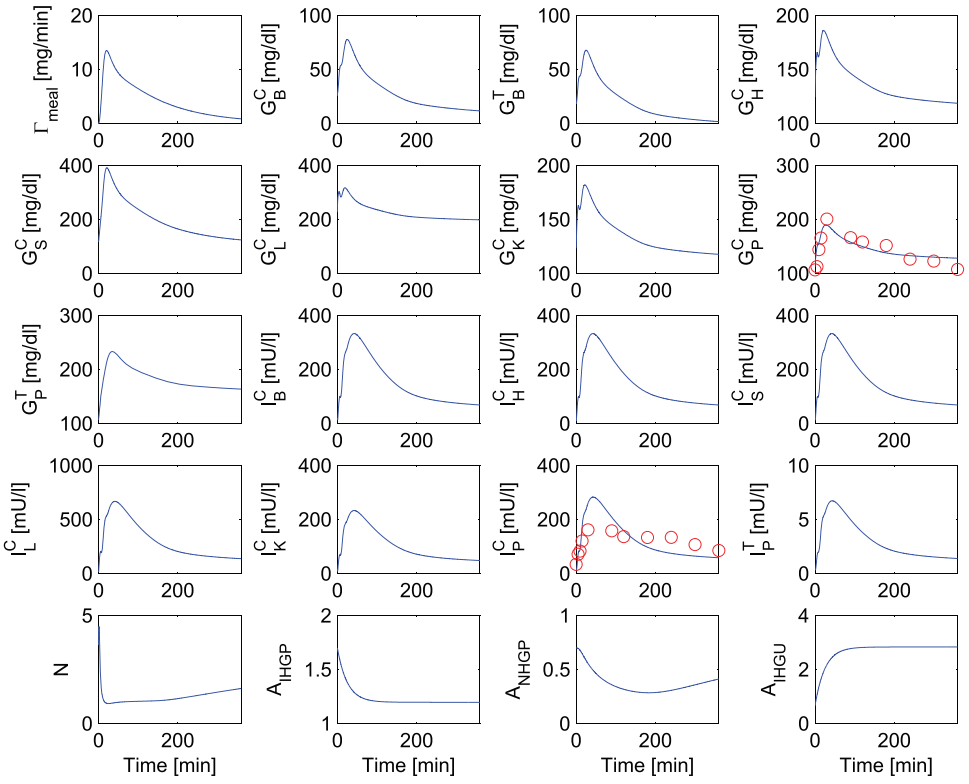


**Fig. 2.** Simulation of Sorensen's model scaled to normal rat after a 1.8827 g meal.

## 4. Results

In this section the objective is to make a representative comparison between the predictions of the simulator for a healthy human subject of 70 kg and a rat of average weight of 277 g. Hence, equivalent intakes to both species must be taken into account in order to rigorously evaluate the results. Therefore, since the experimental data of the rats were obtained for a meal intake of 1.8827 g, the corresponding meal intake for the healthy human model (Sorensen, 1985) is calculated with Eq. (4) giving the equivalence of 31.44 g. Then, a first interesting conclusion is reached by analyzing both rat and human dynamic behaviors shown at Figs. 1 and 2. As can be seen the simulated evolution during 350 min of both models (rat and human) are qualitatively and quantitatively similar as expected.

A second interesting conclusion is reached when confronting the experimental average data of blood glucose and insulin concentration after the glucose load with the rat model predictions which are in good agreement. To see in more detail the evolution of these measured variables Figs. 3 and 4 can be seen. In Table 10 the result of the measurements used to validate and to adjust the healthy rat model is presented. The procedure conducted to measure blood glucose and insulin in rats is described in Appendix B.

These results were obtained after applying the methodology exposed in Section 2 and adjusting the hyperbolic tangent functions parameters of Table 9 (Section 2.2) to the average data of Table 11. The first subplot from the grid corresponds to the rate of glucose appearance calculated with the model proposed by Dalla Man et al. (2006), Eq. (A.5). From subplot number 2–20, the figures represent the states of the model of Sorensen (from Eqs. (A.11)–(A.29)). The points in red are real measurements from the laboratory of capillary blood glucose and insulin concentration. They represent the mean values of the measurements of 10 healthy rats (Table 11).Blood glucose concentration units is mg/dl and insulin mU/l.

**Table 9**
Metabolic rate functions parameters.

| Parameter | Rats | Humans |
|---|---|---|
| $A_{\Gamma_{IPGU}}$ | 5.4207 | 7.03 |
| $B_{\Gamma_{IPGU}}$ | −8.5803 | −6.52 |
| $C_{\Gamma_{IPGU}}$ | 0.3878 | 0.338 |
| $D_{\Gamma_{IPGU}}$ | −5.8131 | −5.82 |
| $A_{\Gamma_{IHGP}}$ | 1.2566 | 1.21 |
| $B_{\Gamma_{IHGP}}$ | 0.0611 | 1.14 |
| $C_{\Gamma_{IHGP}}$ | 1.0637 | 1.66 |
| $D_{\Gamma_{IHGP}}$ | 0.7062 | −0.89 |
| $A_{\Gamma_{NHGP}}$ | 0 | 0 |
| $B_{\Gamma_{NHGP}}$ | −2.3128 | −2.7 |
| $C_{\Gamma_{NHGP}}$ | 0.7460 | 0.39 |
| $D_{\Gamma_{NHGP}}$ | 0 | 0 |
| $A_{\Gamma_{GHGP}}$ | 1.3243 | 1.42 |
| $B_{\Gamma_{GHGP}}$ | 3.3519 | 1.41 |
| $C_{\Gamma_{GHGP}}$ | −0.3629 | 0.62 |
| $D_{\Gamma_{GHGP}}$ | −0.5889 | −0.497 |
| $A_{\Gamma_{IHGU}}$ | 0 | 0 |
| $B_{\Gamma_{IHGU}}$ | −2.8302 | −2 |
| $C_{\Gamma_{IHGU}}$ | 1.8123 | 0.55 |
| $D_{\Gamma_{IHGU}}$ | 0 | 0 |
| $A_{\Gamma_{GHGU}}$ | 1.9487 | 5.66 |
| $B_{\Gamma_{GHGU}}$ | −9.3751 | −5.66 |
| $C_{\Gamma_{GHGU}}$ | 1.4483 | 2.44 |
| $D_{\Gamma_{GHGU}}$ | −0.7634 | −1.48 |
| $A_{\Gamma_{GPNR}}$ | 0.6844 | 2.93 |
| $B_{\Gamma_{GPNR}}$ | 6.6733 | 2.1 |
| $C_{\Gamma_{GPNR}}$ | 2.7705 | 4.18 |
| $D_{\Gamma_{GPNR}}$ | −1.0745 | −0.61 |
| $A_{\Gamma_{IPNR}}$ | 0.8934 | 1.31 |
| $B_{\Gamma_{IPNR}}$ | 0.7421 | −0.61 |
| $C_{\Gamma_{IPNR}}$ | 0.3916 | 1.06 |
| $D_{\Gamma_{IPNR}}$ | −0.8485 | −0.47 |

**Table 10**
Blood glucose and insulin measurements in healthy rats.

| Intake [mg] | Rat ♯1 | | Rat ♯2 | | Rat ♯3 | | Rat ♯4 | | Rat ♯5 | | Rat ♯6 | | Rat ♯7 | | Rat ♯8 | | Rat ♯9 | | Rat ♯10 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Time [min] | 2000 | | 2000 | | 2100 | | 2500 | | 1638 | | 2730 | | 1400 | | 1365 | | 1638 | | 1456 | |
| | G | I | G | I | G | I | G | I | G | I | G | I | G | I | G | I | G | I | G | I |
| 0 | 109.7 | 20.3 | 101.4 | 20.2 | 111.7 | 11 | 92.5 | 40.6 | 114.5 | 13.3 | 123.7 | 61.4 | 115.2 | 18.5 | 107.6 | 122.4 | 100.6 | 10.8 | 86.8 | 14 |
| 5 | 113.7 | 57.4 | 125.6 | 14.1 | 129.4 | 95.3 | 128.7 | 164.7 | 113.8 | 18.5 | 119.7 | 155.3 | 126.8 | 22.1 | 79.3 | 139.4 | 89.2 | 21.4 | 98 | 21.4 |
| 10 | 131.4 | 43.2 | 176.5 | 88.2 | 203.9 | 83.8 | 167.8 | 99.5 | 128.4 | 24.2 | 144.9 | 192.8 | 141.8 | 11.9 | 137.5 | 205.1 | 103.4 | 37 | 104.8 | 37 |
| 15 | 140.9 | 10.9 | 172.7 | 121.2 | 186.7 | 51.5 | 249.6 | 288.1 | 176 | 118.5 | 203.3 | 223 | 157.3 | 25.3 | 115.2 | 277.3 | 107.8 | 43.3 | 143.5 | 43.3 |
| 30 | 162.8 | 14.7 | 192.8 | 95.3 | 200.8 | 347.6 | 176.8 | 174.9 | 229.6 | 106.7 | 197.1 | 273.5 | 271 | 43.6 | 132.9 | 360.2 | 126.6 | 97.2 | 315 | 97.2 |
| 90 | 141.4 | 52.4 | 145 | 65.2 | 175.6 | 514.1 | 161.1 | 242.6 | 134.6 | 32.9 | 243.7 | 167.6 | 200 | 11.3 | 135.4 | 416.3 | 113.8 | 36.7 | 210.3 | 36.7 |
| 120 | 146.1 | 22.4 | 132.6 | 144.2 | 166 | 320.5 | 180.7 | 187.4 | 133.1 | 22.9 | 225.1 | 157.2 | 148.2 | 13.8 | 161.9 | 347.4 | 136.1 | 72.2 | 149.7 | 72.2 |
| 180 | 142.6 | 17.8 | 121 | 13.1 | 169.7 | 196.9 | 173.9 | 245.4 | 118.1 | 15.7 | 176.2 | 274.3 | 149.8 | 26.1 | 143.4 | 413 | 111.7 | 63.9 | 207.9 | 63.9 |
| 240 | 120.5 | 101.4 | 93.9 | 13.3 | 171.5 | 256.1 | 114.1 | 98.4 | 93.2 | 14.3 | 131.3 | 216.6 | 86.3 | 6.7 | 143.3 | 436.9 | 144.1 | 94.7 | 165 | 94.7 |
| 300 | 103.3 | 35.8 | 96.8 | 9.4 | 156.8 | 49.8 | 122.6 | 173.3 | 108 | 2.8 | 118.7 | 194.4 | 103.2 | 19.5 | 132.2 | 391.9 | 138.4 | 95.1 | 146.2 | 95.1 |
| 360 | 106.5 | 35.3 | 89.6 | 11.9 | 131.7 | 114.3 | 112.1 | 164.3 | 57.7 | 2.1 | 106.5 | 175.6 | 94.9 | 8.9 | 123.7 | 260 | 125.2 | 38.5 | 124.3 | 38.5 |

**Table 11**
Average experimental data from 10 healthy rats.

| Time [min] | 0 | 5 | 10 | 15 | 30 | 90 | 120 | 180 | 240 | 300 | 360 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Plasma insulin [mU/l] | 33.3 | 71 | 82.3 | 120.2 | 161.1 | 157.6 | 136 | 133 | 133.3 | 106.7 | 84.9 |
| Plasma glucose [mg/dl] | 106.4 | 112.4 | 144 | 165.3 | 200.5 | 166.1 | 158 | 151.4 | 126.3 | 122.6 | 107.2 |
| Oral glucose [mg] | 1882.7 | – | – | – | – | – | – | – | – | – | – |

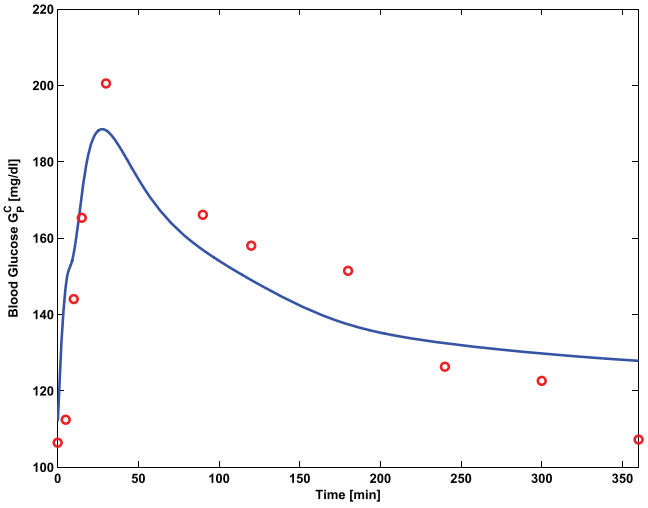


**Fig. 3.** Blood glucose concentration of 10 normal rats after an oral glucose intake.

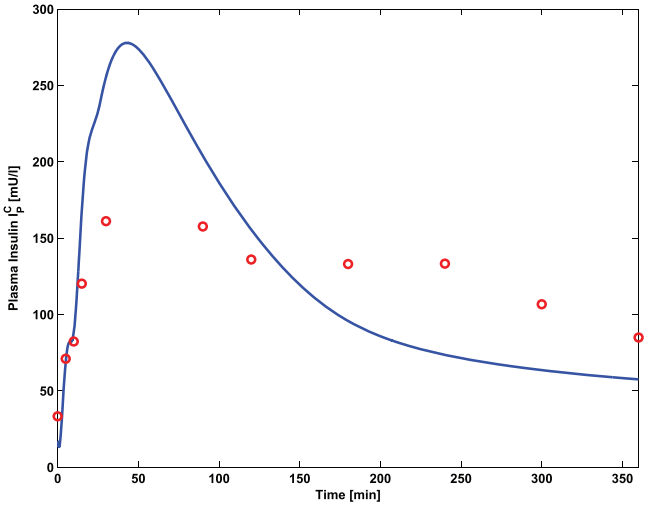


**Fig. 4.** Blood insulin concentration of 10 normal rats after an oral glucose intake.

Both models (human and rat) were implemented for simulation purposes in Matlab R2012b, version 8.0.0.783, under a Windows 7 64 bits interface on an Intel Core i7-3770 CPU 3.40 GHz. The integration method was a variable-step ode15s (stiff/NDF) and the elapsed time for the optimization problem was 206.47904 s.

## 5. Conclusions and future work

Scaling procedures in Chemical Engineering are very useful to extrapolate the conclusions drawn at the pilot plant to a large industrial process. In terms of biological research the rats have been studied since long time ago to better understand different physiological mechanism in the human body. Therefore, based on the usefulness of the scaling techniques in the context of Chemical Engineering one of the main contributions of this work is to propose a systematic procedure to find the relationship between the endocrine system of healthy rats and humans. The main difference between industrial chemical plants and biological systems is that the size and volume of organs and blood flow rates have not to be estimated. They only have to be measured by some specific technique. Hence, one of the steps proposes how to determine the model parameters transformation between both species. Therefore, the physical parameters for rats were obtained thanks to an exhaustive search in the literature. Then, assuming similar metabolic behavior between humans and rats and taking into account our own laboratory experience and an intensive experimental work with ten healthy rats, it was possible to obtain reasonable parameters, using Simplex method, to fit the predictions of the simulator with real data.

In this context, it can be considered that some aspects of this work can be improved by testing with a more sophisticated optimization technique which could drive to better adjusted parameters. The assumption of equivalent meal intake based on the relationship of oxygen consumption can be replaced by other option equally suitable for comparison purposes. According to the obtained results, it can be said that the assumptions adopted to do this preliminary scale up procedure seems to be in good direction. Then, the other main contribution of this work is to present the first results of a successfully adapted model of a healthy rat from the healthy version of the well known Sorensen's endocrine system model for human beings. Moreover, a systematic methodology for quantifying the analogies between humans and rats has

been proposed. It is important to note that, as regards the blood glucose, insulin and glucagon interaction within the human body, the authors did not find other reported results about this interesting task. Although this is a first approach to handle this problem, the proposed method can be extrapolated to other animals (Hall et al., 2012) and also to different case studies. In accordance with Sorensen (1985), this model and the scale up procedure is valid for an average adult healthy human being of 70 kg and an average adult healthy Sprague Dawley rat of 277 g of body weight.

As could be seen, the evolution of the rat model is qualitatively and quantitatively similar to the model of humans as expected. The next logical step would be to contrast the results with more experimental data from the laboratory. In particular, those variables which were not confronted with laboratory measurements could be part of the future work of our group that has been carried out experiments related to the endocrine system of rats since 7 years ago. Additionally, some of the hypothesis raised here could be thoroughly tested and confirmed.

Another future work will be adapting the model of Sorensen and the methodology proposed here to the type I diabetic version of the simulator. The main possible use of this model would be to help on the diabetes problem from a technological point of view, serving as a simulator of specific diabetic subjects which could be used to extrapolate the results to specific diabetic patients. Moreover, a model with such characteristics could be really useful to predict human responses when experimenting with rats. Consequently, safety procedures can be conducted. It is important to remark that the selection of Soresen model to do the scale up gives the possibility to use it as an observer. Hence, the model is able to predict the evolution of concentrations in every organ of the full body, all of which are very difficult to measure in vivo. Another very important application would be to test different drugs in the endocrine system of rats, be them healthy or diabetic, and extrapolate the effects on the human body more accurately.

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## Appendix A. The mathematical model

The rate of glucose appearance ($\Gamma_{meal}$) of Dalla Man et al. (2006) is modeled by a three-compartment model:

$$\dot{Q_{sto1}}(t) = -k_{gri}Q_{sto1}(t) + d(t) \tag{A.1}$$

$$\dot{Q_{sto2}}(t) = -k_{empt}(t, Q_{sto}(t))Q_{sto2}(t) + k_{gri}Q_{sto1}(t) \tag{A.2}$$

$$\dot{Q_{gut}}(t) = -k_{abs} + k_{empt}(t, Q_{sto}(t))Q_{sto2}(t) \tag{A.3}$$

$$Q_{sto}(t) = Q_{sto1}(t) + Q_{sto2}(t) \tag{A.4}$$

$$\Gamma_{meal} = fk_{abs}Q_{gut}(t) \tag{A.5}$$

where $Q_{sto}$ (mg) is the amount of glucose in the stomach (solid, $Q_{sto1}$, and liquid phase, $Q_{sto2}$), $Q_{gut}$ (mg) is the glucose mass in the intestine, $k_{gri}$ is the rate of grinding, $k_{abs}$ is the rate constant of intestinal absorption, $f$ is the fraction of intestinal absorption which actually appears in plasma, $d(t)$ (mg/min) is the amount of ingested glucose, $\Gamma_{meal}$ (mg/kg/min) is the glucose rate of appearance in plasma and $k_{empt}$ is the rate constant of gastric emptying which is a time-varying nonlinear function of $Q_{sto}$.

From Sorensen (1985), the equations for glucose dynamics are:

$$\dot{G_B^C} = (G_H^C - G_B^C)\frac{q_B}{v_B^C} - (G_B^C - G_B^T)\frac{v_B^T}{T_B v_B^C} \tag{A.6}$$

$$\dot{G_B^T} = (G_B^C - G_B^T)\frac{1}{T_B} - \frac{\Gamma_{BU}}{v_B^T} \tag{A.7}$$

$$\dot{G_H^C} = (G_B^C q_B + G_L^C q_L + G_K^C q_K + G_P^C q_P - G_H^C q_H - \Gamma_{RBCU})\frac{1}{v_H^C} \tag{A.8}$$

$$\dot{G_S^C} = (G_H^C - G_S^C)\frac{q_S}{v_S^C} + \frac{\Gamma_{meal}}{v_S^C} - \frac{\Gamma_{SU}}{v_S^C} \tag{A.9}$$

$$\dot{G_L^C} = (G_H^C q_A + G_S^C q_S - G_L^C q_L)\frac{1}{v_L^C} + \frac{\Gamma_{HGP}}{v_L^C} - \frac{\Gamma_{HGU}}{v_L^C} \tag{A.10}$$

$$\dot{G_K^C} = (G_H^C - G_K^C)\frac{q_K}{v_K^C} - \frac{\Gamma_{KE}}{v_K^C} \tag{A.11}$$

$$\dot{G_P^C} = (G_H^C - G_P^C)\frac{q_P}{v_P^C} + (G_P^T - G_P^C)\frac{\Gamma_{v_P^T}}{T_P^G v_P^C} \tag{A.12}$$

$$\dot{G_P^T} = (G_P^C - G_P^T)\frac{1}{T_P^G} - \frac{\Gamma_{PGU}}{v_P^T} \tag{A.13}$$

Equations for insulin dynamics:

$$\dot{I_B^C} = (I_H^C - I_B^C)\frac{Q_B}{V_B^C} \tag{A.14}$$

$$\dot{I_H^C} = (I_B^C Q_B + I_L^C Q_L + I_K^C Q_K + I_P^C Q_P - I_H^C Q_H)\frac{1}{V_H^C} \tag{A.15}$$

$$\dot{I_S^C} = (I_H^C - I_S^C)\frac{Q_S}{V_S^C} \tag{A.16}$$

$$\dot{I_L^C} = (I_H^C Q_A + I_S^C Q_S - I_L^C Q_L)\frac{1}{V_L^C} + \frac{\Gamma_{PIR}}{V_L^C} - \frac{\Gamma_{LC}}{V_L^C} \tag{A.17}$$

$$\dot{I_K^C} = (I_H^C - I_K^C)\frac{Q_K}{V_K^C} - \frac{\Gamma_{KC}}{V_K^C} \tag{A.18}$$

$$\dot{I_P^C} = (I_H^C - I_P^C)\frac{Q_P}{V_P^C} + (I_P^T - I_P^C)\frac{V_P^T}{T_P^I V_P^C} \tag{A.19}$$

$$\dot{I_P^T} = (I_P^C - I_P^T)\frac{1}{T_P^I} - \frac{\Gamma_{PC}}{V_P^T} \tag{A.20}$$

The related metabolic sink terms are:

$$\Gamma_{LC} = F_{LC}(I_H^C Q_A + I_S^C Q_S + \Gamma_{PIR}) \tag{A.21}$$

$$\Gamma_{KC} = F_{KC} I_H^C Q_K \tag{A.22}$$

$$\Gamma_{PC} = \frac{I_P^T}{(1 - F_{PC})/(F_{PC}Q_P) - (T_P^I)/(V_P^T)} \tag{A.23}$$

and the remaining 4 equations of Sorensen's model are:

$$\dot{N} = (\Gamma_{PNR} - N)\frac{F_{PNC}}{V_N} \tag{A.24}$$

$$\dot{A_{IHGP}} = \frac{1}{T_I}\left\{\Gamma_{IHGP} - A_{IHGP}\right\} \tag{A.25}$$

$$\dot{A_{NHGP}} = \frac{1}{T_R}\left[\Gamma_{NHGP} - A_{NHGP}\right] \tag{A.26}$$

$$\dot{A_{IHGU}} = \frac{1}{T_I}\left[\Gamma_{IHGU} - A_{IHGU}\right] \tag{A.27}$$

$$\Gamma_{KE} = \begin{cases} 71 + 71\tanh[0.011(G_K^C - 460)] & \text{for} \quad G_K^C < 460 \\ 0.872G_K^C - 330 & \text{for} \quad G_K^C \geq 460 \end{cases} \tag{A.28}$$

Other metabolic rates causing addition or removal of mass were assigned mathematical equations of the general form:

$$\Gamma_e = \{A_{\Gamma_e} - B_{\Gamma_e}\tanh[C_{\Gamma_e}(x_i + D_{\Gamma_e})]\} \tag{A.29}$$

The subscript $i$ in Eq. (A.29) is the state vector element involved in the metabolic effect, and subscript $e$ denotes specific effects within the model: the effect of glucose on hepatic glucose production *GHGP*, the effect of glucose on hepatic glucose uptake *GHGU*, the effect of insulin on peripheral glucose uptake *IPGU*, the effect of glucose on pancreatic glucagon release *GPNR* and the effect of insulin on pancreatic glucagon release *IPNR*. The pancreatic insulin release model ($\Gamma_{PIR}$) used in Sorensen's model was developed by Landahl and Grodsky (1982), originally developed for rats and in Sorensen's Ph.D. thesis adjusted to human data.

$$\Gamma_{PIR} = \frac{S(G_H^C)}{S(G_H^B)}\Gamma_{PIR}^B \tag{A.30}$$

$$\dot{P} = \alpha[P_\infty - P] \tag{A.31}$$

$$\dot{I} = \beta[X - I] \tag{A.32}$$

$$\dot{Q} = K(Q - Q_0) + \gamma P - S \tag{A.33}$$

$$S = [M_1 Y + M_2(X - I)]Q \tag{A.34}$$

$$X = \frac{(G_H^C)^{X_{01}}}{(G_0)^{X_{01}} + X_{03}(G_H^C)^{X_{02}}} \tag{A.35}$$

$$P_\infty = Y = (X)^\delta \tag{A.36}$$

## Appendix B. Experimental procedures

### B.1. Animals

Experiments were carried out in female Sprague Dawley rats of $277 \pm 20$ g body weight, fed with balanced food (GEPSA, Pilar, Córdoba, Argentina) and tap water *ad libitum*. The animals room had a dark/light cycle of 12h/12h and temperature of $23 \pm 1$ degree centigrade. Blood samples were obtained from the vein of the tail in heparinized tubes; they were centrifuged and plasma was saved at −20 degrees centigrade to measure glucose and insulin concentrations. All experiments were performed in accordance with the international ethical guidelines of animal care National Institute of Health (1986), Olfert et al. (1993). The protocol was approved by the Ethics Committee, School of Medicine, Rosario National University.

### B.2. Glucose oral administration

Animals with 8 h of fast received glucose (0.6 g/100 g body weight) by orogastric tube. Blood samples were obtained before and after glucose intake (0, 5, 10, 15, 30, 90, 120, 180, 240, 300, 360 min).

### B.3. Glucose measurement

Glucose concentration was spectrophotometrically measured with a commercial kit (Wiener Laboratorios, Rosario, Argentina) in a Perkin–Elmer lambda 11 spectrophotometer.

### B.4. Insulin measurement

Measurement of blood insulin levels were carried out by RIA using a commercial kit (Ria kit Rat insulin, Millipore Corporation, Billerica, MA, USA).

### B.5. Oxygen measurement

Oxygen consumption was measured with a Clark-type electrode (Gilson, Middleton, USA). In vivo $VO_2$ measurement was carried out for 10 min to obtain basal $VO_2$ (Fina et al., 2012). $VO_2$ in human beings was recorded with the same electrode and a facemask.

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