Model for evaluation of data from oral glucose tolerance test

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In the present study, a frequently sampled Oral Glucose Tolerance Test (OGTT) was performed in healthy volunteers. Subsequently, on the basis of measured data, a mathematical model was developed, capable to account for the effect of the gastric-emptying process on glycemia in OGTT. The model performance is exemplified by results of model fits to the measured glucose concentration-time profiles in plasma of the volunteers. The modeling results revealed that the volunteers could be divided into three groups: The volunteers of the first group which exhibited high values of the apparent clearance of glucose, i.e. 0.63±0.08 l/min (arithmetic mean ± standard deviation), and two glucose fractions sequentially disposable for absorption. The volunteers of the second group which exhibited medium values of the apparent clearance of glucose, i.e. 0.28±0.18 l/min, and three glucose fractions sequentially disposable for absorption. Finally, the volunteers of the third group which exhibited low values of the apparent clearance of glucose, i.e. 0.06±0.02 l/min, and three glucose fractions sequentially disposable for absorption. In the first group, the first and second fraction of glucose disposable for absorption ranged 47.8–98.8 and 1.2–52.2% of the glucose dose, respectively. In the second group, the first, second, and third fraction of glucose fraction disposable for absorption ranged 6.1–70.4, 22.4–76.0, and 3.0–70.1% of the glucose dose, respectively. In the third group, the first, second, and third fraction of glucose fraction disposable for absorption ranged 20.5–95.6, 3.9–51.6, and 0.5–31.9% of the glucose dose, respectively.

Key words: OGTT, gastric emptying, model, time delay, system approach.

MODEL PRE VYHODNOTENIE DÁT ZÍSKANÝCH V ORÁLNOM GLUKÓZOVOM TESTE

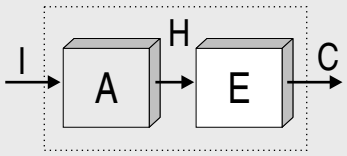
V práci bol vykonaný často vzorkovaný orálny glukózový test (OGTT) u zdravých dobrovoľníkov. Následne na základe nameraných dát bol vyvinutý matematický model, ktorý umožňuje vystihnúť vplyv procesu gastrického vyprázdňovania na glykémiu v OGTT. Funkčnosť modelu je ukázaná na príkladoch znázorňujúcich ako model umožnil získať aproximácie nameraných koncentračných profilov glukózy v plazme u dobrovoľníkov. Z výsledkov modelovania vyplýva že dobrovoľníkov bolo možné rozdeliť do troch skupín: Dobrovoľníci prvej skupiny vykazovali vysoké hodnoty zdanlivej clearance glukózy, t.j. 0,63±0,08 l/min (aritmetický priemer ± štandardná odchylka), a dve frakcie glukózy ktoré boli postupne k dispozícii pre absorpciu. Dobrovoľníci druhej skupiny vykazovali stredné hodnoty zdanlivej clearance glukózy, t.j. 0,28±0,18 l/min, a tri frakcie glukózy ktoré boli postupne k dispozícii pre absorpciu. Dobrovoľníci tretej skupiny vykazovali nízke hodnoty zdanlivej clearance glukózy, t.j. 0,06±0,02 l/min, a tri frakcie glukózy ktoré boli postupne k dispozícii pre absorpciu. V prvej skupine dobrovoľníkov, prvá frakcia glukózy ktorá bola k dispozícii pre absorpciu bola v rozsahu 47,8–98,8 a druhá frakcia v rozsahu 1,2–52,2% dávky glukózy. V druhej skupine dobrovoľníkov, prvá frakcia glukózy ktorá bola k dispozícii pre absorpciu bola v rozsahu 6,1–70,4, druhá 22,4–76,0 a tretia 3,0–70,1% dávky glukózy. V tretej skupine dobrovoľníkov, prvá frakcia glukózy ktorá bola k dispozícii pre absorpciu bola v rozsahu 20,5–95,6, druhá 3,9–51,6 a tretia 0,5–31,9% dávky glukózy.

Kľúčové slová: OGTT, gastrické vyprázdňovanie, model, časové oneskorenie, systémový prístup.

Introduction

In our previous work[(1)], we introduced a circulatory physiologically-based model, proposed for the evaluation of data obtained in the Intra Venous Glucose Tolerance Test.

Fig. 1. System H that represents an idealized behavior of a substance in the body after a single oral dose of this substance.



I – input of substance, C – concentration profile of substance, A – absorption subsystem, E – elimination subsystem

The objective of the present study is to develop a model for the evaluation of data from the Oral Glucose Tolerance Test (OGTT), capable to account for the effect of the gastric-emptying process[(2-5)] on glycemia in OGTT. OGTT is a screening test that involves measurement of an individual's plasma glucose levels after he/she drinks a solution containing 75 grams of glucose. This test is commonly used to confirm diagnosis of diabetes mellitus or gestational diabetes and to diagnose other metabolic diseases[(6)].

Theory

Fig. 1 schematically shows an idealized behavior of a substance in the body after a single oral dose of this substance. Namely, in the given figure it is assumed that the substance is disposable for absorption and elimination immediately after

its input into the body. The symbol ***I*** stands for the single oral dose of the substance and the symbol ***C*** stands for the resultant concentration-time profile of the substance in the body. The idealized behavior of the substance after the single oral dose can be represented by the two subsystems connected in serial, as shown in Fig. 1. In the given figure, absorption of the substance is represented by the absorption subsystem (denoted by the symbol ***A***) and elimination of the substance by the elimination subsystem (denoted by the symbol ***E***). The subsystems and connected in serial form the system ***H*** that represents the idealized behavior of the substance in the body after the single oral dose of this substance. The concentration-time profile of the substance that results from the idealized behavior of the substance after the single oral dose can be described by the very well known model[1]

Eg. 1

$$C(t)=a(e^{-\alpha t}-e^{-\beta t})$$

which is called the Bateman function in the field of biomedicine[7]. In Equation 1, **C(t)** is the model of the concentration-time profile of the substance, **t** is time, and **a,** α and β are the coefficients of the Bateman-function model. In the field of bio-medicine, a concentration-time profile of a substance that can appropriately be approximated by the model in the form of Equation 1 is considered a regular profile. In contrast to Fig. 1, Fig. 2 illustrates a non-idealized behavior of a substance in the body after a single oral dose of this substance. Namely, in the given figure it is assumed that the behavior of the substance after the single oral dose is influenced by the gastric retention of several fractions of the oral substance dose, due to the delayed gastric-emptying process. As a result, several fractions of the oral substance dose are sequentially, or in other words time-dependently, disposable for absorption. In Fig. 2, the time-dependent disposal of the substance for absorption is represented by the subsystem denoted by the symbol **TD** and the non-idealized behavior of the substance in the body after the single oral dose is represented by the system **H**. As seen, in the given case the system **H** is formed by the subsystems **TD**, **A**, and **E**, connected in serial. Consequently, the model expressed by Equation 1 cannot be employed to approximate the concentration-time profile of the substance that results in the body from the single oral dose of the substance in the situation shown in Fig. 2. Fig. 3 exemplifies the situation in OGTT. The symbols $\mathbf{f_1}$ and $\mathbf{f_2}$ denote two fractions of the oral glucose dose which are sequentially disposable for absorption, namely the fractions of the oral glucose dose which sequentially pass from the stomach to the small intestine. Fig. 4 exemplifies the same situation as does Fig. 3, however in a more abstract way than does the latter figure. The plot in the left part of this figure illustrates the single oral dose of glucose, which is denoted by the symbol $\mathbf{I_g}$. The given glucose input into the body can mathematically be described as the product of the glucose dose **D** and the Dirac delta function δ**(t)**[8-11]. Upper part of Fig. 4 illustrates the system $\mathbf{H_g}$ that represents the behavior of glucose in the body in OGTT. As seen, the glucose input into the body is considered the input of the system and the resultant concentration-time profile $\mathbf{C_g}$ of glucose in plasma is considered the output of the system $\mathbf{H_g}$. Analogously to the system illustrated in Fig. 2, the system $\mathbf{H_g}$ consists from the subsystems **TD**, **A**, and

Fig. 2. System that represents a non-idealized behavior of a substance in the body after a single oral dose of this substance, i.e. the behavior which is influenced by the delayed gastric-empting process. The meaning symbols I, A, E and C is the same as that in Fig. 1.

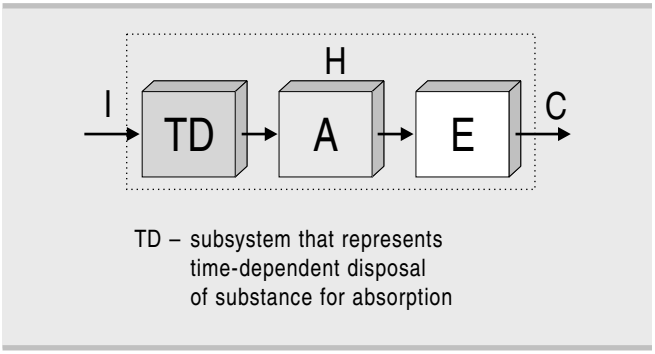


Fig. 3. Introductory figure to the oral glucose tolerance test. f_1, f_2 – the fractions of glucose which successively disposable for absorption.

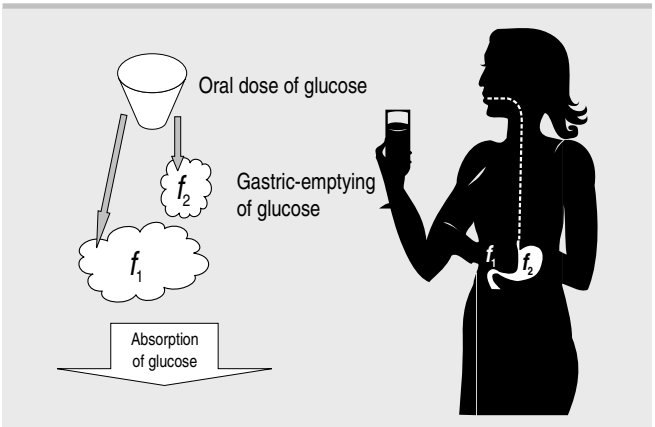


Fig. 4. System Hg that represents the behavior of glucose in the body in the oral glucose tolerance test. Ig – the glucose input into the body. Cg – the resultant concentration-time profile of glucose in plasma. D – the oral glucose dose. δ(t) – the Dirac delta function. The meaning of the symbols f_1, f_2 is the same as that in Fig. 3. R – the rate of the disposal of the glucose fraction for absorption. τ_1 and τ_2 – the time delay of the disposal of the first and second glucose fraction respectively for absorption. t_1 and t_2 – time of the end of the disposal of the first and second glucose fraction respectively for absorption. The meaning of other symbols is analogous to that in Fig. 2.

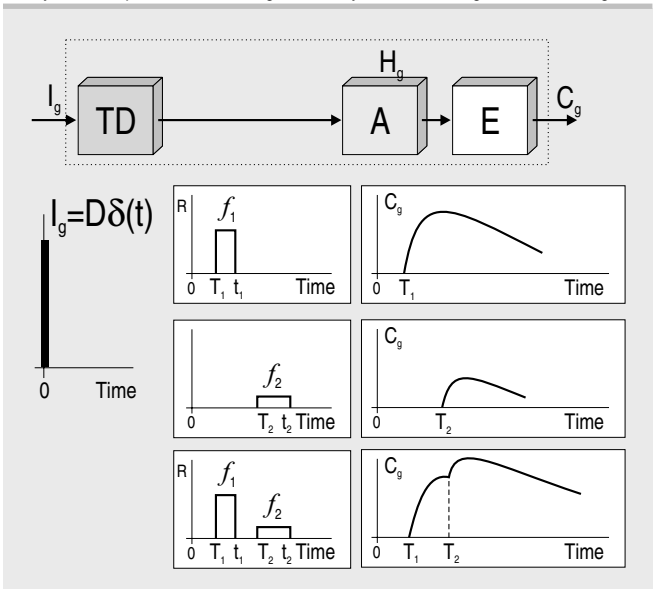
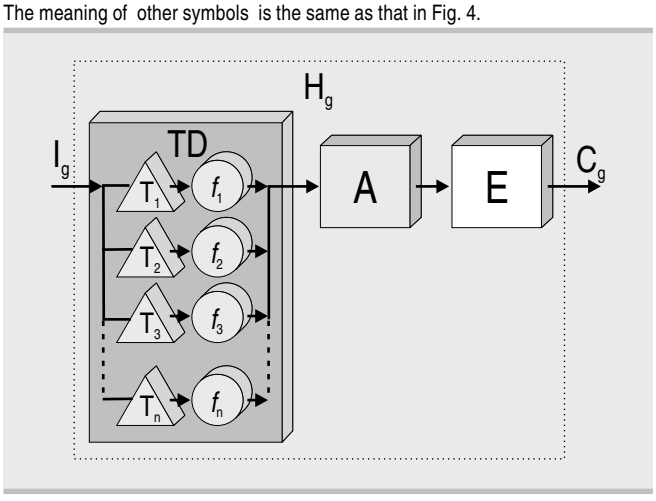


Table 1.

Subject	Sex	Age (year)	Height (cm)	Body mass (kg)	BMI (kg/m^2)	Waist (cm)	Hip (cm)	WHR (-)
Ms	M	28	1.92	72	19.5	75	92	0.82
An	M	22	1.87	76	21.7	80	91	0.88
A1	F	30	1.65	52	19.1	67	91	0.74
R0	M	28	1.78	73	23.0	82	95	0.86
Fa	M	29	1.92	87	23.6	86	102	0.84
K1	F	24	1.77	70	22.3	79	100	0.79
Pg	F	23	1.60	54	21.1	71	91	0.78
Mb	F	26	1.67	52	18.6	66	88	0.75
Ri	M	27	1.97	76	19.6	76	95	0.80
S1	F	33	1.69	70	24.5	84	104	0.81
Mi	M	23	1.78	69.5	21.9	85	90	0.94
S0	F	27	1.65	53	19.5	63	93	0.68
Ma	F	25	1.68	55	19.5	67	90	0.74
Arithmetic mean		27	1.76	66.1	21.2	73.5	94	0.8
Standard deviation		3.3	0.12	11.5	1.9	7.9	5	0.07

E, connected in serial. The middle part of Fig. 4 exemplifies the time dependent disposal of glucose for absorption in OGTT. The glucose fraction $\mathbf{f_1}$ is disposable for absorption over the time interval starting at time τ_1 and ending at time t_1. This fraction undergoes absorption and elimination in the body, or in other words it passes through the absorption subsystem **A** and the elimination subsystem **E** of the body. In the end, this fraction produces the concentration-time profile of glucose in plasma that starts at time τ_1, see the right part of Fig. 4. The latter profile has the form of a time-delayed Bateman function. Analogously, the glucose fraction f_2 is disposable for absorption over the time interval from time τ_2 to time t_2. The fraction f_2 of glucose undergoes absorption and elimination in the body in the identical way as does the glucose fraction f_1, or in other words the glucose fraction f_2 passes through the same absorption and elimination subsystem of the body as does the glucose f_1. The glucose fraction f_2 produces the concentration-time profile of glucose in plasma that starts at time τ_2 and that also has the form of a time-delayed Bateman function. Correspondingly, the two successive glucose fractions f_1 and f_2 produce the concentration-time profile of glucose in plasma that exhibits a shape considered an irregular shape in the field of bio-medicine, namely the shape of a sum of two time-delayed Bateman-functions. In general, the delayed gastric-emptying process may yield several successive fractions of glucose dose that are disposable for absorption at successive times in OGTT. This may result in a more complex concentration-time profile of glucose in plasma than that illustrated in Fig. 4. To quantify several successive fractions of glucose, the structure illustrated in Fig. 5 can be employed for the subsystem of the system H_g. The given structure assumes n fractions f_i of glucose disposable for absorption at n successive time points τ_i, where i=1, 2, ..., n. Finally, to account for all the processes that play predominant role in the behavior of glucose in OGTT, the subsystem LC can be added to the structure of the system H_g, as depictured in Fig. 6. The latter subsystem represents the cessation of the glucose output from the liver which is the consequence of the increased concentration of insulin in plasma[1, 12]. Correspondingly, the input of the subsystem LC is the concentration-time profile C_{in} of insulin in plasma. In Fig. 6, the model elements of the subsystem TD (representing the fractions of the glucose dose that are sequentially disposable for absorption) are denoted by the symbols F_i. Correspondingly, these model elements are characterized by the time delays τ_i, the times t_i, and the glucose fractions f_i.

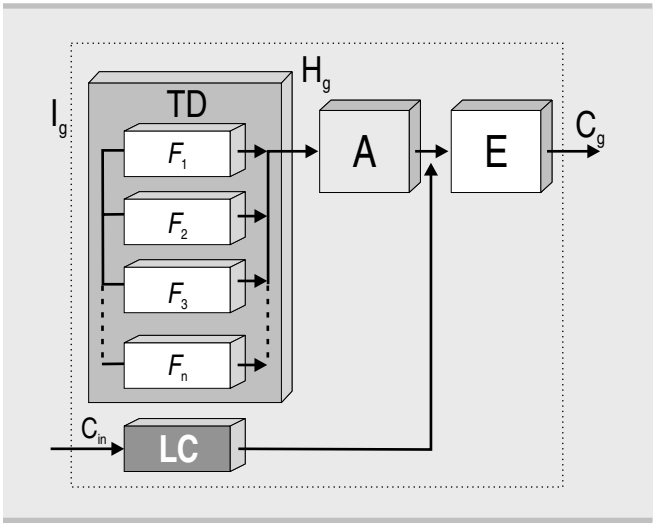
Fig. 5. System H_g and structure of TD subsystem. f_i – the glucose fraction. τ_i – the time delay of the disposal of the glucose fraction for absorption. I=1,2,...,n. The meaning of other symbols is the same as that in Fig. 4.



Material and methods

Thirteen healthy nonsmokers with no family history of diabetes (see Table 1) participated in this study. OGTT was performed using the American Diabetes Association Expert Committee criteria[13]. The volunteers were instructed to abstain from alcohol, caffeine, and strong physical activity for 24 h and to fast for 12 h before investigation day. After an explanation of the experimental procedure, a written voluntary consent was obtained from each volunteer. The study protocol was approved by the Ethic Committee of the Institute of Experimental Endocrinology, Slovak Academy of Sciences.

Fig. 6. System H_g and the LC subsystem that represents the cessation of the glucose output from the liver, as a consequence of the increased concentration of insulin in plasma. F_i – model element that represents time-dependent disposal of the glucose fraction for absorption, i=1,2,...,n. C_{in} – the concentration-time profile of insulin in plasma. The meaning of other symbols is the same as that in Fig. 4.



The investigation started at 8:00 A.M. The volunteer was asked to rest in a comfortable armchair for 30 min. An indwelling catheter (Surflo-W Terumo, Belgium) was inserted into the antecubital vein of the volunteer for blood sampling. At time zero, the volunteer drank a solution containing 75 grams of anhydrous glucose diluted in 250 ml of water over 1–2 min. The blood samples for the measurement of the glucose and insulin concentration in plasma of the volunteer were drawn 15 min before the glucose load, at the time point of the glucose load, and 8, 15, 22, 30, 45, 60, 90, 120, 140, 160, and 180 min after the glucose load.

The samples were centrifuged at 4°C, and after the separation of aliquots of plasma the aliquots were stored frozen at -20 °C until analyzed. The plasma glucose concentration was measured using the glucose oxidize method (Boehringer Manheim, Germany). The plasma insulin concentration was measured employing the conventional IRMA kit (Imunotech France)[1].

To determine the optimal structure of the models of the system H_g (see Fig. 6) of the volunteers enrolled and to estimate parameters of the models of the given system as well as of the apparent clearance of glucose, the integrated software package CTDB (Clinical Trials Database) was employed[14]. In the modeling procedure, the subsystems A and E of the system H_g of the volunteer were modeled using first-order models without time delays[1, 8-11]. The model elements F_i of the subsystem TD of the system H_g of the volunteer were approximated using time-delayed pulses that exhibited the magnitudes R_i. The given pulses started at times τ_i and ended at times t_i. Equation 2 held for each glucose fraction f_i[2].

Eg. 2

$$f_i = R_i(t_i - \tau_i)$$

The meaning of the magnitude is the rate at which glucose is disposable for absorption. The sum of all the glucose fractions was equal to one, as expressed by Equation 3[3].

Eg. 3

$$\sum_{i=1}^{n} f_i = 1$$

The subsystem LC the system H_g of the volunteer was modeled using a first-order model with the time delay τ_{in} and the gain parameter G_{in}[1, 8-11]. The time delay τ_{in} is time of the beginning of the decrease of the glucose concentration in plasma that results from the cessation of the glucose output from liver[12], which is caused by the increased insulin concentration in plasma. The gain parameter G_{in} determines the decrease of the glucose concentration in plasma that corresponds to the increase of the insulin concentration in plasma by 1 mU/l. U stands for the international unit of insulin[13].

Results

The modeling results of the all volunteers enrolled in this study are summarized in Table 2. These results revealed the volunteers enrolled in this study could be divided into the three groups. The first group consisted from the 5 volunteers, i.e. volunteers Ms, An, A1, R0, and Fa. The subsystem TD of these volunteers contained two model elements F (see Fig. 6), i.e. the two fractions of the glucose dose were sequentially disposable for absorption in these volunteers. In the given group, the first and second fraction of glucose disposable for absorption ranged from 47.8 to 98.8 and from 1.2 to 52.2% of the glucose dose, respectively. The volunteers of the given group exhibited the highest values of the parameter G_{in}, i.e. 1.36±0.09 mmol/mU (arithmetic mean ± standard deviation), and simultaneously they exhibited the highest values of the apparent clearance of glucose, i.e. 0.63±0.08 l/min, see Table 3. The second group consisted from the 4 volunteers, i.e. volunteers K1, Pg, Mb, and Ri. In contrast to the volunteers of the first group, the subsystem TD of the volunteers of the second group contained three model elements F, i.e. the three fractions of the glucose dose were sequentially disposable for absorption in the volunteers. In the given group, the first, second, and third fraction of glucose fraction disposable for absorption ranged from 6.1 to 70.4, from 22.4 to 76.0, and from 3.0 to 70.1 % of the glucose dose, respectively. The volunteers of the given group exhibited the medium

Table 2.

Subject	f_1 (%)	τ_1 (min)	t_1 (min)	f_2 (%)	τ_2 (min)	t_2 (min)	f_3 (%)	τ_3 (min)	t_3 (min)	τ_{in} (min)	G_{in} (mmol/mU)	Cl (l/min)
Ms	49.3	3.2	8.4	50.7	25.0	30.0				99.9	1.23	0.91
An	72.9	1.6	10.6	27.1	20.0	22.2				99.5	1.35	0.70
A1	98.8	3.3	19.9	1.2	22.3	23.0				37.2	1.15	0.61
R0	65.4	1.8	19.6	34.6	23.2	38.7				44.3	1.38	0.48
Fa	47.8	2.3	14.9	52.2	18.6	28.3				58.4	1.70	0.43
K1	70.4	2.4	11.6	22.4	19.2	23.3	7.2	65.5	67.9	92.6	0.83	0.52
Pg	6.1	1.6	5.3	23.8	17.4	25.4	70.1	40.3	54.9	41.6	0.08	0.30
Mb	21.0	3.2	19.2	76.0	56.1	93.7	3.0	130.7	135.9	108.0	0.09	0.15
Ri	8.3	2.2	10.9	52.3	14.3	42.7	39.4	87.2	113.9	30.8	0.26	0.13
S1	30.8	3.2	27.5	37.3	59.4	101.0	31.9	119.0	153.0	65.0	0.07	0.09
Mi	55.4	3.1	29.8	43.1	31.2	52.3	1.5	84.6	88.1	84.6	0.02	0.06
S0	95.6	2.2	33.7	3.9	52.3	53.9	0.5	113.9	114.3	>150	<0.01	0.06
Ma	20.5	2.3	26.8	51.6	27.6	68.4	27.9	65.3	111.4	143.1	0.10	0.03
Aritmetic mean	49.4	2.5	18.3	36.6	29.7	46.4	22.6	88.3	104.9	75.4	0.69	0.34
Standard deviation	30.8	0.6	8.9	20.9	15.6	26.7	24.5	31.1	33.1	34.6	0.64	0.28

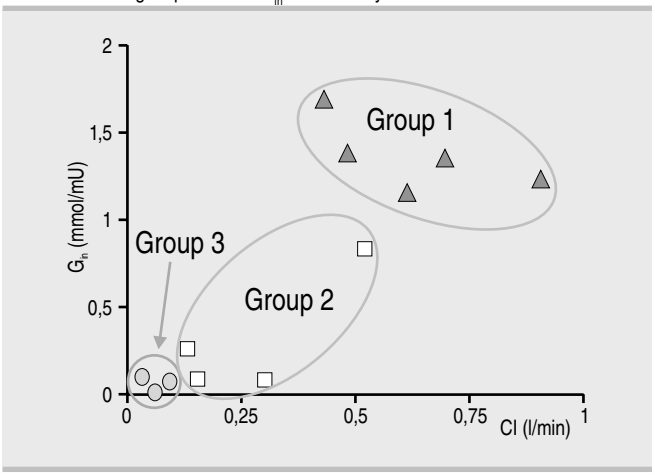
Table 3.

Group	Gin (mmol/mU)	Cl (l/min)
1	1.36±0.09*	0.63±0.08
2	0.32±0.35	0.28±0.18
3	0.06±0.04	0.06±0.02
*All the vaules: Arithmetic mean ± standard deviation		

values of the parameter G_{in}, i.e. 0.32±0.35 mmol/mU, and simultaneously they exhibited the medium values of the apparent clearance of glucose, i.e. 0.28±0.18 l/min, see Table 3. Finally, the third group consisted from the 4 volunteers, i.e. volunteers S1, Mi, S0, and Ma. Analogously to the second group, the subsystem TD of the volunteers of the third group contained also three model elements F, i.e. the three fractions of the glucose dose were sequentially disposable for absorption in the volunteers. However, in contrast to the second group, the volunteers of the third group exhibited the lowest values of the parameter G_{in}, i.e. 0.06±0.04 mmol/mU, and they simultaneously exhibited the lowest values of the apparent clearance of glucose, i.e. 0.07±0.01 l/min, see Table 3. In the third group, the first, second, and third fraction of glucose fraction disposable for absorption ranged from 20.5 to 95.6, from 3.9 to 51.6, and from 0.5 to 31.9% of the glucose dose, respectively. The relation between the values of the apparent clearance of glucose and the parameter G_{in} of the subsystem LC of the volunteers of all the three groups is presented in Fig. 7.

To illustrate plots of the modeling results, volunteer A1 of the first group and volunteer S0 of the third group were arbitrarily selected as representatives. The plots of the fractions of the glucose dose which were sequentially disposable for absorption in the representative volunteers A1 and S0 are shown in Fig. 8. Fig. 9 portrays the measured concentration-time profiles of glucose in plasma of the representative volunteers A1 and S0 and the fits of these profiles obtained as the responses of the models of the system H_g of these volunteers to the glucose input I_g. Fig. 10 illustrates the measured concentration-time profiles of insulin in plasma of the representative volunteers A1 and S0.

Fig. 7. The relation between the values of the apparent clearance of glucose Cl and those of the gain parameter G_{in} of the subsystem LC of the volunteers.



Discussion

The apparent clearance of glucose CI is a surrogate the uptake of glucose by many cells of the body after the glucose dose[1, 12]. The gain parameter G_{in} of the subsystem LC (see Fig. 6) is a surrogate of the cessation of the glucose output from liver, which is the consequence of the elevated concentration of insulin in plasma and which yields to the time-delayed decrease of the glucose concentration in plasma[1, 12].

The percentages of the glucose dose which were at the first place disposable for absorption in the representative volunteers A1 and S0 were very close (98.8 and 95.6%) and so were the times of the start of the disposal of these fractions (3.3 and 2.2 min), see Table 2. On the contrary, however, the disposal of the first fraction of the glucose dose for absorption of volunteer A1 took 16.6 min but that of volunteer S0 took markedly longer, i.e. 31.5 min. This was the consequence of the fact that the rate at which the first glucose fraction was disposable for absorption in volunteer A1 was markedly higher than that in volunteer S0, as shown in Fig. 8. The percentages

Fig. 8. Plots of the fractions of the oral dose of glucose which are sequentially disposable for absorption. Volunteer A1 (thick line). Volunteer S0 (thin line).

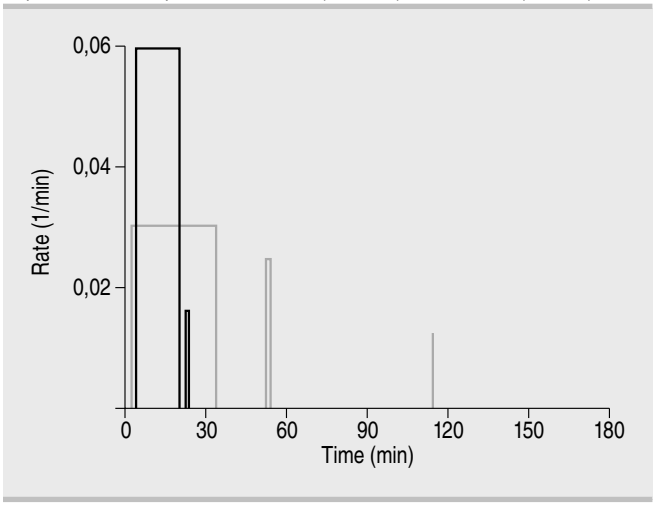


Fig. 9. Measured glycemia after the oral dose of glucose. Volunteer A1 (squares). Volunteer S0 (circles). Approximations of the given profiles by the outputs of the models of the system H_g of the volunteers.

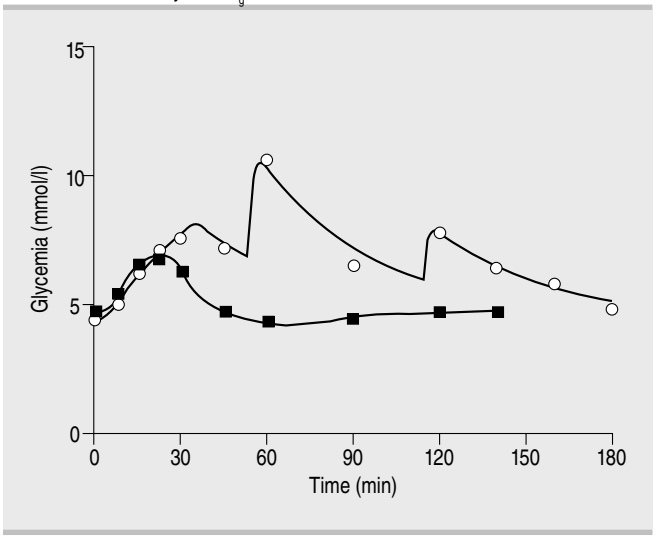
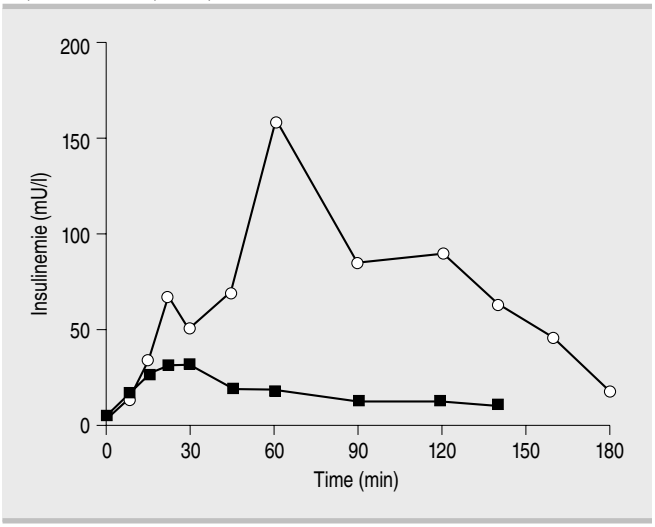


Fig. 10. Measured insulinemia after the oral dose of glucose. Volunteer A1 (squares). Volunteer S0 (circles).



of the glucose dose which were in the second place disposable for absorption in both volunteers in volunteers A1 and S0 were 1.2 and 3.9 %, respectively. The disposal of the second fraction of the glucose dose in volunteer A1 started at 22.3 min but that in volunteer S0 started markedly later, i.e. at 52.3 min. In contrast to volunteer S0, volunteer A1 did not exhibit the third fraction of the glucose dose disposable for absorption. Finally, volunteer S0 exhibited the markedly lower value of apparent celarance of glucose than did volunteer A1. As follows from Table 2, the subjects enrolled in this study exhibited the great intra-individual variability.

In clinical practice, the influence of the gastric-emptying process can led to false negative results of OGTT. The main contribution of the procedure described in the current study is the fact that this procedure enables to model influences of the gastric-emptying process on OGTT, using the authors' software package CTDB (Clinical Trial DataBase). A version of this package is available at the www site given in reference[14]. However, for the modeling of the influences of the gastric-emptying process in OGTT, the sampling schedules of glycemia and isulinemia must be minimally as frequent. as those used in the current study.

Modeling methods commonly used in the field of bio-medicine are based on fitting diverse regression functions to measured concentration-time profiles of substances in the body. These procedures do not take into consideration input profiles of substances into the body. On the contrary, the identification methods used in our work, see e. g. works [1, 8–11], and in the present study are aimed at selecting such model structures that on the introduction of mathematically described inputs of substances into the body originate the responses fitting the measured concentration-time profiles of substances in the body.

The present article is predominantly aimed at permitting assimilation of the presented ideas by non-mathematically trained readers. Thus details of the modeling techniques employed are not given. The modeling procedure used in this study may contribute to the working library of the modeling techniques used in the field of bio-medicine since the given procedure enables to account for the effect of the gastric-emptying process on glycemia in OGTT. As it follows from the previous works, see e.g. studies[2, 3] and also from the very recent works[4, 5], understanding of the given effect may be a key to achieving glucose control in diabetes. The reason for this is that the gastric-emptying process is one of the major determinants of the glucose responses to oral carbohydrates.

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