Introduction

Since the early 1970s, mathematical models of the glucose control of the insulin secretion have attracted considerable attention. These models are predominantly aimed at providing a characterization of parameters called the insulin-sensitivity parameters, which are considered the key parameters of glucose – insulin interaction. Among these models the most frequently used models are the classic minimal model (MINMOD) and its recent variants for the Intra Venous Glucose Tolerance Test (IVGTT). IVGTT consists of injecting intravenously a glucose dose and frequently sampling glucose and insulin plasma concentrations afterwards, for a period of about three hours (2–4, 9–11).

The given models yield the insulin-sensitivity parameters whose physiological interpretation is ambiguous (10) and so are their units. The fitting of MINMOD on the available data has to be conducted in separate steps, as the proposing authors of MINMOD specifically stated (11). However, glucose – insulin interaction, or in other words the glucose-insulin system, actually is an integrated physiological system of the body and so naturally a unified model of this system would be desirable (5).

The processes involved in glucose – insulin interaction after the glucose load can be schematically illustrated as shown in Fig. 1 (12).

Key words: glucose-insulin interaction, circulatory model, time delay, system approach.

Circulatory model for glucose – insulin interaction after intravenous administration of glucose to healthy volunteers

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In the current study, glucose – insulin interaction was investigated on the basis of measured data obtained by the intravenous glucose tolerance test (IVGTT) in healthy subjects. The study objective was to propose a circulatory physiologically-based model of glucose – insulin interaction, capable of quantifying processes that develop in the body after the glucose load, i.e. the glucose uptake by body cells and cessation of the glucose output from liver. The proposed model is a new alternative to the classic minimal model and its recent variants, which are currently in the use for the evaluation of measurements from IVGTT. Examples are given, showing results of the fits of the proposed model to measured plasma concentration-time profiles of glucose of the subjects enrolled.

Key words: glucose-insulin interaction, circulatory model, time delay, system approach.

CIRKULAČNÝ MODEL INTERAKCIE GLUKÓZA-INZULÍN PO INTRAVENÓZNOM PODÁNÍ GLUKÓZY ZDRAVÝM DOBROVOĽNIKOM

V tejto práci bola študovaná interakcia glukózy a inzulínu na základe meraných údajov získaných v standardnom intravenóznom tolerančnom teste glukózy u zdravých dobrovoľníkov. Bol vyvinutý cirkulačný model popisujúci interakciu glukóza – inzulín, ktorý umožňuje kvantifikovať procesy nastávajúce v tele po podaní dávky glukózy, t.j. vychytávanie glukózy bunkami tela a prerušenie výstupu glukózy z peče. Prezentovaný cirkulačný model je novou alternatívou ku klasickému minimalnému modelu a k jeho nedávne modifikovaným verziam, v súčasnosti používaným pre vyhodnotenie meraní z intravenóznych toleraných testov glukózy. Uvedené príklady ukazujú aproximácie meraných časových závislostí koncentrácie glukózy u dobrovoľníkov, ktoré sú získané pomocou vyvinutého cirkulačného modelu.

Kľúčové slová: interakcia glukóza-inzulín, cirkulačný model, časové oneskorenie, systémový prístup.
2. The cessation of the glucose output from liver leads to the decrease of glucose concentrations in plasma, which is denoted as Effect 2 in Fig. 1. However, MINMOD and its recent variants, enable neither to quantify Effect 1 nor Effect 2. To overcome the problems with MINMOD and its recent variants given above, the objective of the present study was to propose a unified physiologically-based model of the glucose-insulin system, capable of quantifying Effects 1 and 2 of the glucose load.

**Theory**

Fig. 2 schematically shows the human body in IVGTT. Glucose is administered intravenously into the right cubital vein and the sampling for determination of glucose and insulin concentrations in plasma is performed in the left cubital vein. Considered from an anatomical point of view, the interconnection of the principal body organs and tissue regions by the blood circulation can be illustrated as shown in Fig. 3. On the other hand, considered form a system-approach point of view, the same interconnection can be depicted as given in Fig. 4. The latter figure can be redrawn into Fig. 5. As seen, except for a schematic illustration of the injection and sampling site (R. arm and L. arm respectively), the latter figure shows a version of the well known classic physiologically-based model, commonly used in pharmacokinetics. The given model consists from several branches, which are interconnected by arterial flows as inputs and venous flows as outputs. To build up such a classic physiologically-based model of behavior of a substance in the body the following a priori information is needed:

1. information on volumes of the principal body organs and sizes of the principal tissue regions
2. information on blood flows through the principal body organs and tissue regions
3. information on concentration-time profiles of the substance in the principal body organs and tissue regions.

In the case of IVGTT, however, such information is not available. To overcome this problem, tools of the dynamic-system theory can be employed to propose a circulatory

**Fig. 2.** Proposed scheme of the human body showing an intravenous load of glucose and the blood sampling for the determination of glucose and insulin concentrations in plasma. a) Principal interior organs of the human body. b) Brain and venous and arterial blood flows.

**Fig. 3.** Proposed scheme of the anatomical interconnection of the principal organs and extremities of the human body by the blood circulation.

**Fig. 4.** Proposed scheme of the interconnection of the principal organs and extremities of the human body by the blood circulation, based on the system approach.

**Fig. 5.** Classic physiologically-based model (1), modified by the indication of the administration and sampling sites.
physiologically-based model of the glucose-insulin system in the case of IVGTT. The model proposed in this study consists from several paths interconnected by arterial and venous flows similarly as does the classic physiologically-based model shown in Fig. 5. In contrast to the latter model, however, the paths of the proposed circulatory model of the glucose-insulin system contain components called subsystems, which represent either body organs or tissue regions, predominant for glucose – insulin interaction. An example of such a subsystem is illustrated in the middle part of Fig. 6. The given subsystem is characterized by the following four parameters: The mean residence time \( MRT \) of glucose, the parameter \( g \) that relates the subsystem outlet and inlet concentration of glucose at steady state, the plasma flow \( Q \), and the time-delay parameter \( \tau \), which represents time between the entrance of the concentration-time profile of glucose into the subsystem and appearance of the concentration-time profile of glucose at the output side of the subsystem. The function of the given subsystem can be explained as follows. Let us assume that the parameter \( g \) of the subsystem is equal to 0.5 (i.e. \( C_{\text{out}} < C_{\text{in}} \)) and that the shape of the inlet concentration-time profile of glucose is as shown in part a of Fig. 6. If the transit of glucose through the subsystem is extremely fast (i.e. both \( MRT \) and the time-delay parameter \( \tau \) are very close to zero), the outlet concentration-time profile of glucose would be as shown in part b of the figure. If the transit of glucose through the subsystem is a slower process than that assumed above but there is no time delay between the inlet and outlet concentration-time profile of glucose (i.e. \( MRT \) has a non-zero value but the time-delay parameter \( \tau \) is zero), the outlet concentration-time profile of glucose would be as depicted in part c of the figure. Finally, if the transit of glucose through the subsystem is a slow process and there also is a time-delay between the inlet and outlet concentration-time profile of glucose (i.e. both \( MRT \) and the time-delay parameter \( \tau \) are non-zero values), the outlet concentration-time profile of glucose would be as depicted in part d of the figure.

The structure and function of the circulatory physiologically-based model of the glucose-insulin system proposed in this study (thereafter the circulatory model, unless otherwise indicated) can be explained by using Figs. 7 and 8. The given model consists from one forward path and five backward paths. The forward path contains the cardiopulmonary subsystem \( CP \) which exhibits \( MRT_{CP} \) close to zero, the parameter \( g_{CP} \) close to one, and the time-delay parameter \( \tau_{CP} \) equal zero. The subsystem \( CP \) is predominantly characterized by the plasma flow \( Q_{CP} \) through this subsystem. The subsystems situated in all the backward paths exhibit non-zero values of \( MRT \) and \( Q \), and the positive values of the parameter \( g \), less than 1. The passage of glucose through the arterial and venous blood in the left arm is represented by the subsystem LA, which exhibits non-zero values of \( MRT_{LA} \) and the time-delay parameter \( \tau_{LA} \) and the parameter \( g_{LA} \) close to one. The intravenously administered glucose in IVGTT is carried almost instantaneously from the right cubital vein to the cardiopulmonary subsystem CP. The blood sampling for the measurement of glucose and insulin concentration-time profiles in plasma is performed in the left cubital vein. Fig. 7 explains the function of the circulatory model over four time periods after the input of the exogenous glucose into the body, i.e. the periods from time zero to times \( \tau_1, \tau_2, \tau_3 \), and \( \tau_4 \), where \( \tau_4 < \tau_3 < \tau_2 < \tau_1 \). Over the period up to time \( \tau_1 \) (see Fig. 7a), the change of the glucose concentration at the sampling site is the consequence of the very fast transit of glucose through the forward path containing the subsystem CP and through the backward path containing the subsystem which is denoted VF, in order to indicate the very fast operation of this subsystem. Since the time-delay parameter \( \tau_{VF} \) of the subsystem VF is zero, the subsystem VF very rapidly returns the exogenous glucose from the arterial to the venous side. The subsystems in the remaining backward paths transit the exogenous glucose more slowly than does the subsystem VF, and thus they return only the basal glucose from the arterial to venous side over the period up to time \( \tau_4 \). The response of the circulatory model to the glucose load over the given period is depicted in Fig. 7a. Over the period up to time \( \tau_1 \) (see Fig. 7b), the change of the glucose concentration at the sampling site is the consequence of the very fast transit of the glucose through the subsystems CP and VF and additionally of the glucose transit through the backward path containing the subsystem denoted 1. In contrast to the subsystem VF, the subsystem 1 exhibits a non-zero value of the time-delay parameter \( \tau_1 \). Since the subsystems in the remaining backward paths transit the exogenous glucose more slowly than do the subsystem VF and 1, these subsystems return only the basal glucose from the arterial to venous side over the period up to time \( \tau_4 \). The response of the circulatory model to the glucose load over the given period is depicted in Fig. 7b. Finally, over the period up to time \( \tau_4 \) (see Fig. 7c), the change of the glucose concentration at the sampling site is the consequence of the very fast transit of the glucose through the subsystems CP, VF and additionally of the glucose transit through subsystems 1, 2, and 3. The time-delay parameter \( \tau_3 \) and \( \tau_4 \).
respectively of the subsystem 2 and 3 exhibits a non-zero value. Since the subsystem in the last backward path transits the exogenous glucose more slowly than do the subsystems VF, 1, 2, and 3, this subsystem returns only the basal glucose from the arterial to venous side over the period up to time $\tau_4$. The response of the circulatory model to the glucose load over the given period is depicted in Fig. 7c. The decrease of the plasma concentration-time profile of glucose over the period from time zero to $\tau_4$ seen in the latter figure is the consequence of Effect 1 caused by the glucose load (see Fig. 1), i.e. of the uptake of glucose by many cells of the body after the glucose load.

Effect 2 of the glucose load (see Fig. 1) starts at time $\tau_I$. The insulin concentration in plasma increases above its basal level and the basal level of glucose decreases, as a consequence of the cessation of the glucose output from the liver. The process of the triggered insulin secretion is represented by the subsystem $I$ in Fig. 8. The latter subsystem exhibits non-zero values of $\text{MRT}_I$ and the time-delay parameter $\tau_I$, and the parameter $g_I$ less than zero\(^{16, 12}\). The input of the subsystem $I$ is the difference between the basal and elevated concentration-time profile of insulin in plasma (see the bottom right window of Fig. 8). The response of the circulatory model to the glucose load and to the difference between the basal and elevated concentration-time profile of insulin in plasma is depicted in the upper right window of Fig. 8 over the whole period of the study. This response is the consequence of both Effect 1 and Effect 2 caused by the glucose load.

### Material and methods

Nine healthy subjects (see Table 1) participated in this study. The subjects ate their habitual diets before the study, were body-mass stable, and were non-medicated. They consumed their last meal at 9:00 P.M. on the day before the study. The subjects were considered to be at steady state
Table 1. Basic characteristics and the estimates of the effects of the glucose load, the plasma flow through the cardiopulmonary subsystem, and the glucose clearance of the subjects enrolled. (BMI – the body mass index, WHR – the waist-to-hip ratio, QCP – the plasma flow through the cardiopulmonary subsystem, Cl – the plasma clearance of glucose, SD – standard deviation.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Sex</th>
<th>Age (year)</th>
<th>Height (cm)</th>
<th>Body mass (kg)</th>
<th>BMI (kg/m²)</th>
<th>Waist (cm)</th>
<th>Hip (cm)</th>
<th>WHR (-)</th>
<th>Effect 1 (l/min)</th>
<th>Effect 2 (g.min/l)</th>
<th>Effect 3 (g.min/l)</th>
<th>Qcp (l/min)</th>
<th>Cl (l/min)</th>
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<tbody>
<tr>
<td>Ri</td>
<td>M</td>
<td>27</td>
<td>1.97</td>
<td>79</td>
<td>20</td>
<td>76</td>
<td>95</td>
<td>0.8</td>
<td>0.87</td>
<td>8.63</td>
<td>16.1</td>
<td>4</td>
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<tr>
<td>An</td>
<td>M</td>
<td>22</td>
<td>1.87</td>
<td>76</td>
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<td>80</td>
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<td>1.92</td>
<td>87</td>
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<tr>
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<td>23</td>
<td>1.6</td>
<td>54</td>
<td>21.1</td>
<td>71</td>
<td>91</td>
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<td>0.93</td>
<td>0</td>
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<tr>
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<td>52</td>
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<td>19.4</td>
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<td>0.67</td>
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<tr>
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<td>52</td>
<td>18.6</td>
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<td>88</td>
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<tr>
<td>Ms</td>
<td>M</td>
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<td>19.6</td>
<td>75</td>
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<td>Average</td>
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<td>1.8</td>
<td>68.4</td>
<td>20.6</td>
<td>75.8</td>
<td>93.9</td>
<td>0.8</td>
<td>0.90</td>
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<td>0.1</td>
<td>17.8</td>
<td>1.4</td>
<td>6.8</td>
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<td>0.03</td>
<td>5.8</td>
<td>7.3</td>
<td>0.6</td>
<td>0.1</td>
</tr>
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</table>

Before the glucose load, the standard IVGTT was performed (3, 4, 11). The glucose dose of 0.3 g/kg was rapidly intravenously injected (less than 1.5 minute) into the right cubital vein. Blood samples were drawn from the left cubital vein for measurement of glucose and insulin concentration-time profiles in plasma. Informed consent was obtained from all subjects. The study protocol was approved by the local ethics committee.

To model the glucose-insulin system of the subjects enrolled in this study, the modeling technology described in studies (3, 4, 11) was used. Employing the given technology and the measured concentration-time profiles of glucose and insulin in plasma of the subject, the circulatory model of the subject was built up, the number N of the backward model paths was determined, and the following model parameters were estimated: the plasma flow $Q_{cp}$ of the cardiopulmonary subsystem CP, the mean residence time $MRT_{cp}$ of the subsystem $CP$, and the plasma clearance $Cl$ of glucose of subject A1, R0, and K1 are given in the bottom left window of Figs. 9a, 9b, and 9c, respectively. Estimates of Effects 1, 2, and 3, the plasma flow $Q_{cp}$ through the cardiopulmonary subsystem $CP$, and the plasma clearance $Cl$ of glucose of subject A1, R0, and K1 are given in the bottom left window of Figs. 9a, 9b, and 9c, respectively. Using the modeling results, Effect 1 and Effect 2 caused by the glucose load (see Fig. 1) in the subject were quantified as given below. Effect 1 that quantifies the glucose uptake by many cells of the body was determined according to Eq. 1.

$$\text{Effect 1} = \sum_{j=1}^{N} \frac{Q_j g_j}{Q_{cp}}$$

Effect 2 that quantifies the decrease of the glucose concentrations in plasma as the consequence of the elevated concentrations of insulin in plasma of the subject was quantified according to Eq. 2 (3), where $\text{Effect(t)}$ is the output of the subsystem I (see Fig. 8).

$$\text{Effect 2} = \int_0^\infty \text{Effect(t)} \, dt$$

Results
To exemplify the plots of the modeling results, the three subjects, i.e. subject A1, R0, and K1, were arbitrarily selected as representatives, see Fig. 9. As seen in the upper right
windows of Figs. 9a, 9b, and 9c, the measured concentration-time profiles of glucose in plasma of the given subjects are well approximated by the responses of the circulatory models developed for these subjects. The given responses take into account both Effect 1 and Effect 2 caused by the glucose load. The estimation of the time-delay parameter \( \tau \) of subject A1 yielded the value of 30 minutes (see the upper left window of Fig. 9a), which indicates that Effect 2 of this subject started 30 minutes after the glucose load. As seen, the subject exhibits a moderate Effect 2. Consequently, if Effect 2 is not taken into account, the difference between the measured concentration-time profile of glucose in plasma of the subject and the response of the circulatory model is small, as seen in the bottom right window of Fig. 9a. The given difference is denoted Effect 3 (see the bottom right window of Fig. 9a) and it was quantified according to Eq. 3

\[
\text{Effect 3} = \int_{\tau}^{\infty} (G_M(t) - G(t)) dt
\]

where \( G_M(t) \) is the response of the circulatory model to the glucose load and \( G(t) \) is the linearly interpolated measured concentration-time profile of glucose in plasma of the subject. As seen in Fig. 9b, subject R0 exhibits not only greater Effect 2 than that of subject A1 but the given effect starts 10 minutes after the glucose load, i.e. earlier than that of subject A1. Correspondingly, subject R0 exhibits a greater Effect 3 than does subject A1. The results obtained for subject K1 are summarized in Fig. 9c. Subject K1 does not exhibit Effect 2 and thus Effect 3 of this subject is zero.

Based on the structure of the proposed circulatory model shown in Figs. 7 and 8, Eq. 4 can be derived for the plasma clearance \( C_l \) of glucose after the intravenous glucose load. Estimates of the plasma clearance \( C_l \) of glucose determined according to Eq. 4 and estimates of the plasma flow \( Q_{cp} \) through the cardiopulmonary subsystem CP determined by the modeling procedure are given in Fig. 9a, 9b, and 9c for subjects A1, R0, and K1, respectively.

The predominant results of the present study, i.e. the estimates of Effect 1, Effect 2, Effect 3, the plasma flows \( Q_{cp} \) through the cardiopulmonary subsystem CP, and the plasma clearance \( C_l \) of glucose, of all the subjects enrolled in this study are listed in Table 1.

Fig. 10 illustrates quantification of Effect 1, Effect 2, and Effect 3 caused by the glucose load.

**Discussion**

The present article explains in an easy-to-follow manner how tools of the dynamic-system theory can be used to get insight into what is going on in IVGTT. However, building of the circulatory models of the glucose-insulin systems is a time-consuming and knowledge-based procedure. The physiological meaning of the subsystems identified in the backward paths of the circulatory models of the subjects has to be further elaborated.
The present article is predominantly aimed at permitting assimilation of the presented ideas by non-mathematically trained readers. Thus modeling details are kept to a bare minimum and several illustrative examples are given.

Conclusions
Mathematical models of glucose-insulin interactions continue to develop toward new approaches and this development has the great potential for clinical investigators and therapists. The reason of this is that the exact knowledge of the physiological basis of these interactions is inevitable for the quantitative assessment of the relevant factors controlling these interactions, targeting special diabetic patient populations, and consequently for promoting the safe and effective therapy. As exemplified in the present study, the whole self-regulatory glucose-insulin system can be simultaneously considered and modeled to yield a close approximation to the measured glucose concentrations in plasma in IVGTT. The unified circulatory model developed in this study exhibits a structure and yields parameters which diabetologists and physiologists might consider acceptable. However, as any model of a biological system, the developed circulatory model requires further analyses in order to establish completely all its characteristics.

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