Patient-Specific Modeling by 2D and 3D Visual Membrane Petri Nets

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Abstract —A Patient-specific modeling of the glycemia level in patients with type 1 diabetes mellitus by using 2D and 3D Visual Membrane Petri Nets software applications is described. This model allows to calculate the glycemia level in different parts of the human cardiovascular system (systemic circulation, pulmonary circulation, heart, coronary circulation). Our model reflects glycemia level in veins for the following cases: health condition and both the hepatic insulin-resistance and hepatic insulin-sensitivity in patients with type 1 diabetes. It was shown that the hepatic insulin resistance in type 1 diabetes have a protective effect on the progression of microangiopathy in insulin-independent tissues and it is an compensatory phenomenon, but not a pathological one.

Index Terms — glycemia, Patient-specific model, Petri nets, type 1 ,diabete, s 2D and 3D visual modeling.

I. INTRODUCTION

Auto-regulation is a process within many biological systems, resulting from some internal adaptive mechanisms, which work to adjust the systems response to internal and external stimuli. Most biological systems such as cells, human body, organs and tissues show some degree of auto-regulation. This phenomenon are most clearly observed in the regulation of gene networks, cellular response to external stimuli [1], as well as in the kidney, the heart, the brain, the cardiovascular systems, the liver etc [2].

In the last decades a lot of models of complex self-regulating systems, including biology systems, have been proposed. Such models describe fundamental biological processes, which can occur at different level of cellular organization: DNA, gene networks, organelles, membranes and living cells. Another part of models refers to tissues, organs, organ systems or human body [3, 4].

Different extensions of P systems (so called membrane systems [3]) are proposed to create, using the concept of membrane systems, specific formal models of membrane biological systems that describe real world systems at both at the DNA, living cell, and at tissues, organs, human body level of organization.

In this paper a Patient specific model of complex auto-regulated biological compensatory mechanism is described. Modeling and simulation are performed by both 2D and 3D Visual Membrane Petri Nets software applications [4]. This model allows to calculate the glycemia level in different parts of the human cardiovascular system (systemic circulation, pulmonary circulation, heart, coronary circulation). Our model reflects different glucose concentrations (on the empty stomach) in veins for the following cases: health condition and both the hepatic insulin-resistance and hepatic insulin-sensitivity in patients with type 1 diabetes.

Simulation results of the patient specific model demonstrate the functioning of a compensatory mechanism (auto-regulated process), which maintains the basal level of glycemia (on a empty stomach) in type 1 diabetes on a background of peripheral hyperinsulinemia.

Also, our simulation results confirm that the hepatic insulin resistance in type 1 diabetes may have a protective effect on the progression of microangiopathy in insulin-independent tissues, i.e. it can be considered as an adaptive mechanism, but not a pathological one.

II. VASCULAR LEVELS OF GLYCEMIA

The basis of our model is a theoretical analysis proposed by Dreval to calculate the vascular topography in normal and type 1 diabetes [5]. It is known that the main parameter in the diagnosis of diabetes is the blood glucose level in the peripheral vascular system. On the other hand, the blood sugar concentration or blood glucose level indicates the effectiveness of therapy of diabetes.

In [5], on the basis of experimental data on glucose metabolism in different organs and tissues, a theoretical analysis for the estimation of the glucose concentration in circulation, was proposed. On the basis of this estimations we proposed a dynamical 3D and 2D VMPN Patient specific models to establish the glycemia level in type 1 diabetes patients. Our models can be extended by adding new modules − membrane Pentri nets models that will describe other physiological mechanisms evolved in different organs and tissues. So, integrated Patient specific models were developed. Our model, described in this paper, may explain the tendency of patients with type 1 diabetes to microvascular disease in the eye (retinopathy) and the kidney (nephropathy) - insulin independent organs. This happens due to the fact that in insulin-dependent tissues in type 1 diabetes patients the glucose concentration remains elevated, despite normal level of

glycemia in the peripheral vascular system, available for clinical study. It is known that the minimum deviation (by a few tenths, expressed as mmol / l) from normal values of glycemia predisposes to the development of vascular complications of diabetes.

III. VASCULAR LEVELS OF GLYCEMIA (HEALTH CONDITION)

The theoretical analysis [5] and our model allow to explain what are the levels of glucose in different parts of the vascular blood flow and why the glycemia levels in different inaccessible (for routine clinical studies) parts of the vascular system are different (in type 1 diabetes patients, receiving insulin, , and in healthy persons). On the other hand, the model shows how much differ glucose levels in different parts of the vascular flow in type 1 diabetes patients, receiving insulin, from the normal levels of glycemia.

We propose 3 Pacient specific models to answer these questions - models for vascular glucose basal state (i.e, on an empty stomach) in different parts of the vascular flow. The first model permits to calculate vascular level of glycemia in healthy patients. The second model allows the estimating the concentrations of glucose in different parts of blood circulation in patients with type 1 diabetes with hepatic insulin resistance. The third model is about glycemia levels in type 1 diabetes patients with hepatic insulin sensitivity.

In the basal state, the glucose distribution in the human body depends on the hepatic glucose production. Based on the numerical values of blood flow and glucose extraction percentage in organs and tissues [6], we can calculate the concentration of glucose in different parts of blood circulation. This, in turn, will permit to answer the question of how the blood glucose levels are changed in different parts of the vascular flow, when it is achieved clinical challenge: normalization of glycemia level in peripheral tissues.

For calculation of vascular levels of glucose, the representation of fractional extraction of glucose is used, which is established experimentally for different organs and tissues [5, 6] (Fig. 1). Here the presently known extraction coefficients of glucose (in healthy persons) in peripheral tissues, heart, kidney, liver and brain, as well as the intensity of blood flow are shown.

Fractional extraction of glucose reflects the percentage reduction of blood glucose concentration, when the blood flow irrigates an organ or tissue. The extraction coefficient is calculated as:

$$[(AG-VG)/AG] \times 100, \qquad (1)$$

where AG - arterial glucose, VG - venous glucose.

To calculate the arterial glycemia in the peripheral tissues (for health condition, basal state, i.e. on an empty stomach), using formula (1) we consider that in peripheral veins the blood glucose concentration is 6 mmol / l. Thus, the arterial blood glucose level (because the coefficient of glucose extraction for the peripheral tissues is 3.5%) is 6.21 mmol / l. Note that the arterial blood glucose concentration is the same throughout the vascular blood flow, but, as can be seen in Fig. 1, the venous blood glucose levels in different parts of the vascular system are

different and depend on the coefficients of glucose extraction in target organs and tissues. After calculating the level of glucose in the arterial blood, we can use the known formulas and coefficients to calculate the glycemia level in the venous system of insulin-independent tissues (brain, kidney and heart).
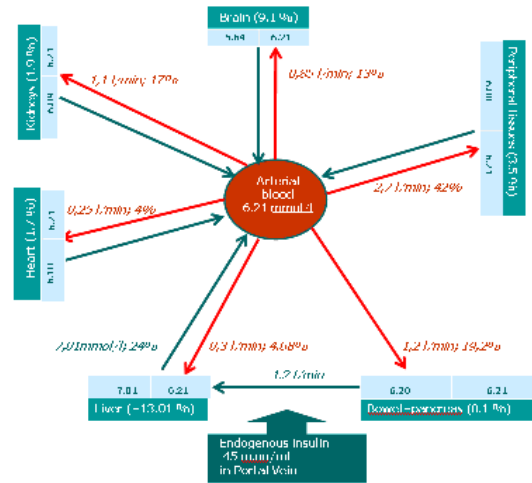

Fig. 1. Schematic representation of the Model of Circulatory Glycemia (health condition).

Obviously, as in the basal state the glucose concentration in the arterial system remains unchanged (6.21 mmol / l), the loss of glucose due to the glucose extraction by tissues and organs, should be offset by a source of glucose production to maintain the arterial blood glucose level at a constant level. Such a compensating source is the liver. In the basal state, the blood glucose concentration, flowing from liver (hepatic vein), higher than inflowing glucose concentration to the liver. This ensures the hepatic compensation of glucose utilization by other tissues, i.e. the maintenance of arterial blood glucose at a constant level.

Therefore, it's need to calculate the concentration of glucose, which must come from the liver into blood stream to compensate for the loss of concentration in other parts of the vascular system.

It's need to calculate the contribution of venous blood glucose levels, flowing from the various organs and tissues in arterial glycemia. This contribution depends not only on the level of glucose in the venous blood, but on the intensity of blood flow in target organs and tissues. Total blood flow is 6.4 l / min: 13% - brain, 17% - kidney, 4% - heart, 23% - liver, 42% - peripherals. So we can calculate absolute (mmol / l) and relative (%) venous blood glucose contributions flowing from the various organs and tissues in the arterial blood glucose concentration.

Now, having the values of flowing to the liver and the hepatic flowing blood glucose concentration, we can calculate the coefficient of hepatic glucose production. Hence the coefficient of hepatic glucose production is 13.4%. Thus, to maintain a constant basal level of glucose the hepatic glucose production coefficient to be 13.4%.

IV. CALCULATION OF VASCULAR LEVEL OF GLYCEMIA IN TYPE 1 DIABETES (HEPATIC INSULIN RESISTANSE)

Type 1 diabetes patients inject insulin into the subcutaneous fat, i.e., into the venous system of the peripheral tissues, from which comes into the systemic circulation (blood stream) and then carried by the arterial system to organs and tissues. In a healthy person the insulin comes in hepatic portal vein and liver partially eliminates the insulin from the blood circulation. As a result, the insulin concentration in the blood flowing from the liver, 2-3 times lower than in the hepatic portal vein. So, in a healthy person the highest concentration of insulin is in the portal vein, and in a patient with diabetes - in the arterial bed.
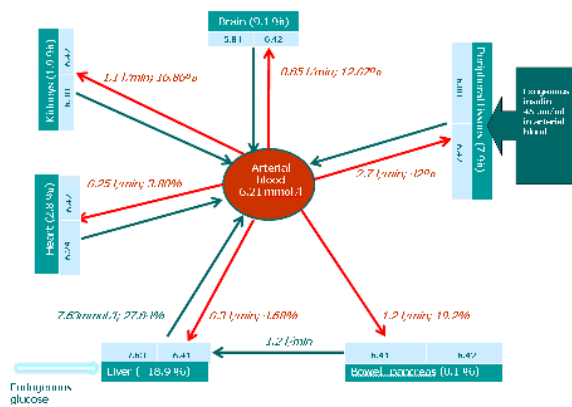
Fig. 2. Schematic representation of the Model of Circulatory Glycemia (hepatic insulin resistance).

The calculations of the vascular level of glycemia in type 1 diabetes are the same as in the case of a healthy person, with the difference that increased insulin concentration in arterial blood provide the growth of glucose extraction coefficients in the insulin dependent tissues (Figure 2). Since the coefficients of the extraction of glucose is higher in this case, for the heart - 2.8% for peripheral tissues, respectively, 7%, hence the arterial blood glucose = 6.42 mmol / L. The algorithm of calculations is identical to that described above in previous paragraph. Comparing the data for this case of hepatic insulin resistancein type 1 diabetes, we can observe that compared with the norm in the venous system of the brain and kidney the blood glucose level increased by 3.38% in the veins of the heart - to 2.22% and in the hepatic vein - to 8.76%. Thus, increase of the difference between arterial and venous blood glucose level in the periphery, will increase glicemia in the venous system in other parts of the vascular flow. On the other hand, due to hyperinsulinemia, glucose extraction in the insulin dependent tissues increased overall by 1.38%. This increase of glucose extraction should be compensated by the liver to maintain the basal state.

V. VASCULAR LEVEL OF GLICEMIA IN TYPE 1 DIABETES WITH HEPATIC INSULIN SENSITIVITY

Let consider the case of peripheral hyperinsulinemia with insulin sensitivity in peripheral tissues and liver. Consider an analogous case with the previous one, when a constant level of glucose in the brachial vein - 6 mmol / l is maintained and the liver is ensure with a normal concentrations of insulin [5].

In the calculations of the balance of glucose in type 1 diabetes, given in previous paragraph, coefficients of elimination of glucose in the insulin-independent tissues, insulin-dependent peripherical tissues and the heart were considered to be predetermined (were fixed). And the production of glucose by the liver was calculated from the condition of maintenance of glycemia at a constant level (basal condition). But now we have to analyze the influence of the risen of hepatic insulin sensibility of at the glucose balance. Taking into account the things told above, we will calculate glycemia levels for the analyzed case. We admit that hepatic sensibility of a type 1 diabetes patient is 10% higher, than it was established in the previous paragraph.

This means that the glucose production by the liver is 10% less that in the previous case, i.e. the coefficient of hepatic glucose production decreased by 10%, from 18.86% to 17%.

The extraction coefficients of glucose for the insulin dependent peripheral tissues and heart are the same as in the previous section. Hence, the arterial blood glucose is 6.42 mmol / l and blood glucose flowing from the heart - 6.24 mmol / l. For simplicity reasons we will assume that the extraction coefficients of the glucose for the gastrointestinal tract is the same as in the case of a healthy patient.

Taking into account the fact that in this case the coefficient of the glucose production by the liver constitutes 17%, glycemia in the hepatic vein will be 7.5 mmol / l. Calculating the absolute weight of the venous glycemia we obtain the following data: hepatic arterial glycemia (1.758 mmol / l), glycemia in the peripheral tissues (2.531 mmol / l) and the heart (0.244 mmol / l).

So, using these data we obtained that the difference of organ contribution of the kidney and brain both of blood flow and extraction glucose coefficients constitute 43% and 57%, respectively, into to the summary contribution of these organs. Thus, the absolute weight (contribution) of the venous glycemia into the brain venous glycemia is 0.787 mmol / l and for the kidney 1.100 mmol / l.

Brain venous glycemia will be 5.92 mmol / l and for the kidney - 6.40 mmol / l. This allows us to calculate the brain extraction coefficient of the glucose 7.7% and for the kidney 0.3%.

Since in case of the hepatic glucose sensitivity (10%) in of type 1 diabetes patients causes the reduction by 0.45% of glucose production compared with hepatic insulin resistance in type 1 diabetes. This decline can not be compensated by peripheral tissues and insulin in heart, since the coefficients of glucose extraction were fixing in these tissues at normal levels. But then, to maintain glycemia at a constant level, the reduction of glucose into the systemic circulation from the liver is compensated for insulin-independent tissues brain and kidney, their extraction coefficients are not fixed a priori. The extraction coefficient for the brain decreased from 9.1 to 7.7%, and for kidneys - from 1.9 to 0.3%. Thus, blood glucose in the venous system of insulin-independent tissues (brain and kidney), increased to a greater extent than in patients with preserved insulin sensitivity only in the peripheral tissues

and heart. This phenomenon should be considered as a compensatory mechanism, which maintains the basal state (constant state of the blood glucose concentration outside of meals and physical exercises) in type 1 diabetes on a background of peripheral hyperinsulinemia.

VI. VMPN PATIENT-SPECIFIC MODEL

The patient-specific model reflects some relevant aspects of the basic auto-regulatory physiological processes from short to long-term adaptation, which evolve in blood and target tissues involved in early stages of type 1 diabetes [6]. Our model of glycemia level in blood circulation was realized in the 2D and 3D Visual Membrane Petri Nets applications (Fig. 3 and Fig. 4).
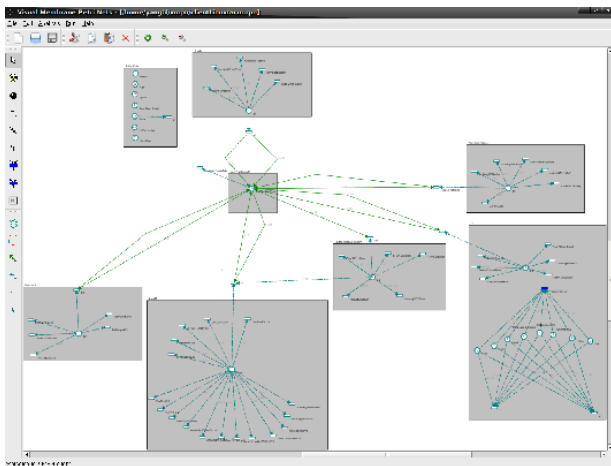
Fig. 3. Screenshot of the 2D VMPN Patient specific

model.

In Fig. 4 it is shown a screensnapshot of the 3D VMPN model of circulatory glycemia level in type 1 diabetes patients.
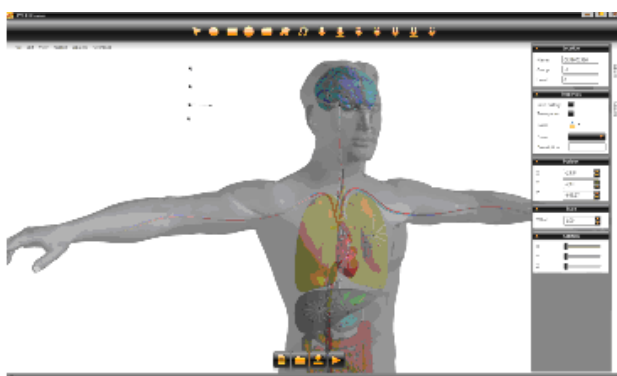
Fig. 4. The main window of the 3D VMPN application.

In these Patient specific models the target organs and tissues are modeled by 2D and 3D elementary membranes, respectively. In the 2D VMPN Patient specific model the skin membrane (which is not represented in the model) corresponds to the vascular system. In the case of the 3D VMPN modeling the skin membrane represents human body and 3D membranes – target tissues: heart, liver, brain, kidney etc.

VII SIMULATION RESULTS

Changes of glycemia level in the insulin-dependent and insulin-independent tissues in the case both of hepatic insulin-resistance and hepatic insulin-sensitivity are demonstrated through simulation.
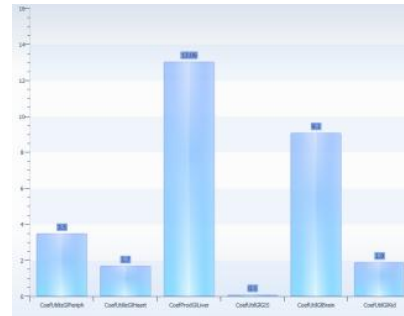

Figure 5. Glucose Utilization/Production Coefficient in Target Organs/Tissues: GIS, Brain, Kidney, Periphery, Heart and Liver, Respectively (*health condition*).

In Figure 5 are presented different values of glucose utilization/ production coefficients in target organs/tissues: periphery (3.5), heart (1.7), liver (13.06), GIS (0.1), brain (9.1), kidney (1.9) for health condition (basal conditions, i.e. on an empty stomach).
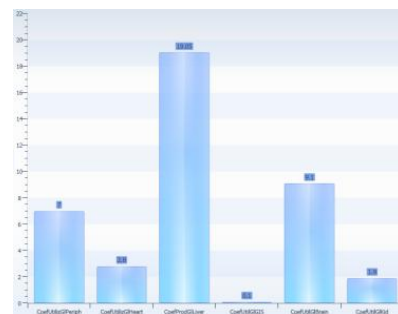

Figure 6. Glucose Utilization/Production Coefficients in Target Organs/Tissues (*hepatic insulin-resistance*).

In Figure 6 are shown different values of glucose utilization/production coefficients in target organs/tissues: periphery (7.0), heart (2.8), liver (19.05), GIS (0.1), brain (9.1) and kidneys (1.9) in the case of hepatic insulin-resistance in patients with diabetes (basal level) in blood vessels (blood insulin level – 45 µmol/l).

Figure 7. Glucose Utilization/Production Coefficients in Target Organs/Tissues (*hepatic insulin- sensitivity* (10%) in patients with type 1 diabetes) (basal level).

Figure 7 shows different values of glucose utilization/production coefficients in target organs/tissues:

periphery (7.0), heart (2.8), liver (17.55), GIS (0.1), brain (7.13) and kidney (0.76) in the case of hepatic insulin-sensitivity (10%) in patients with diabetes (basal level) in blood vessels (blood insulin level – 45 μmol/l).
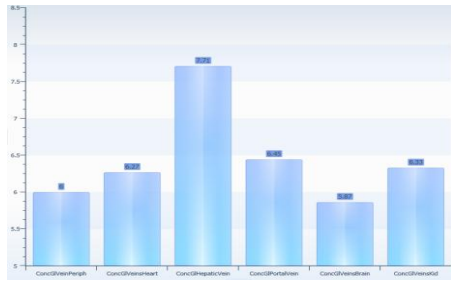

Figure 8. Glucose Concentration Level in Veins (*hepatic insulin-resistance*) in Target Organs/Tissues: Periphery (6 mmol/l), Heart (6.27 mmol/l), Liver (7.71 mmol/l), Portal Vein (6.44 mmol/l), Brain (5.9 mmol/l), and Kidney (6.33 mmol/l).
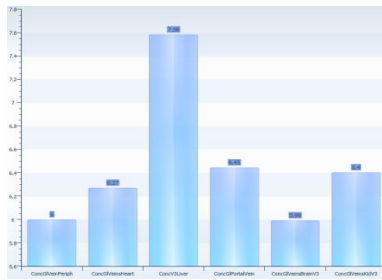

Figure 9. Glycemia Level in Veins (hepatic insulin-sensitivity) in Target Organs/Tissues: Periphery (6 mmol/l), Heart (6.27 mmol/l), Liver (7.58 mmol/l), Portal Vein (6.44 mmol/l), Brain (5.99 mmol/l), and Kidney (6.4 mmol/l).

To maintain the glycemia at a constant level, the reduction of glucose into the systemic circulation from the liver (Fig. 10) is compensated by the insulin-independent tissues (brain and kidney), because their extraction coefficients are not fixed a priori.
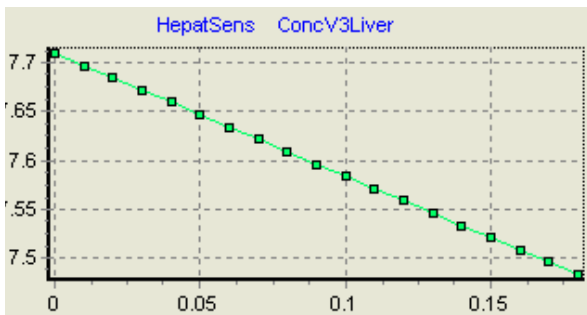

Figure 10. Glycemia Level in Hepatic Veins in dependence on level of hepatic insulin sensitivity.

In Figure 11 it is shown that the glucose extraction coefficient for the brain decreased from 9.1 to 7.7% in dependence on the level of hepatic insulin sensitivity.
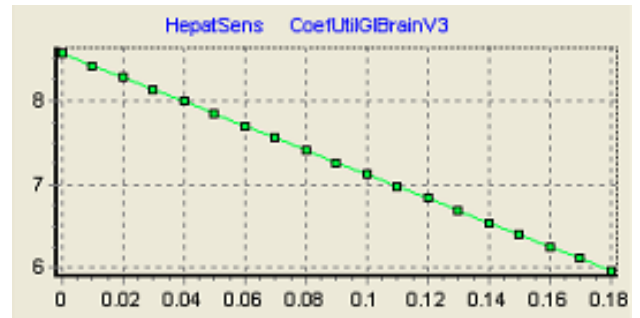

Figure 12. Brain glucose extraction coefficient in dependence on the level of hepatic insulin sensitivity.

Figure 12 shows that the glucose extraction coefficient for kidneys decreased from 1.9 to 0.3% in dependence on the level of hepatic insulin sensitivity.
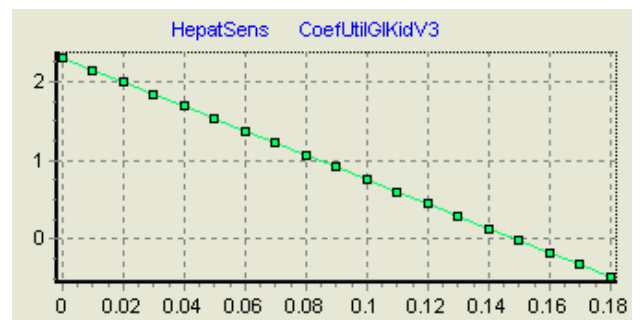

Figure 13. Dependence of kidneys glucose extraction

From the presented calculations it can be seen that insulin-independent tissues are able to compensate for the reduction of hepatic glucose production by no more than 18%. This will lead to inability to maintain the basal state by reducing the consumption of glucose by insulin-independent tissues. And glycemia will inevitably decline in the basal state down to hypoglycemia.

In figures 14 and 15 it is shown that in case of stable basal glycaemia level in type 1 diabetes mellitus the glucose concentrations in veins elevate in insulin-independent tissues (brain, kidney) even if glycaemia level is normal in clinically useful peripheral circulation (6 mmol/l). Thus the model of circulatory levels of glycaemia can explain the predisposal of type 1 diabetes mellitus patients to diabetic retinopathy and nephropathy.
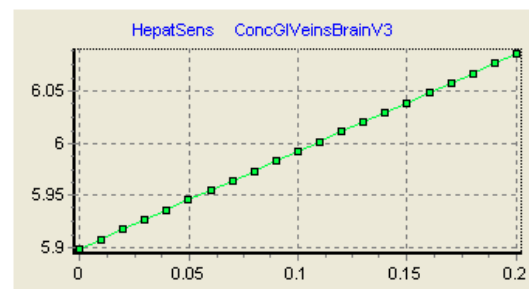

Figure 14. Glycemia Level in Brain Veins in dependence on the level of hepatic insulin sensitivity.

Figures 14 and 15 show that the blood glucose levels in the venous system of insulin-independent tissues (brain and kidney), increased to a greater extent than in

patients with preserved insulin sensitivity only in the peripheral tissues and heart.
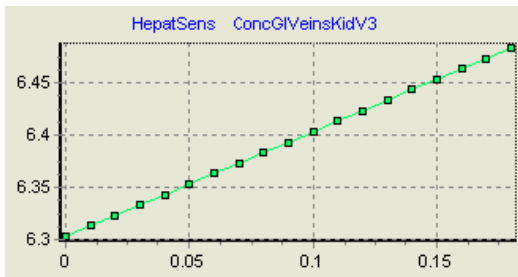

Figure 15. Glycemia Level in Kidneys Veins in dependence on level of hepatic insulin sensitivity.

Thus, it is shown that the glycemia level in the venous system of peripheral tissues and heart has not changed, but hepatic glycemia has decreased.

The reason for the change of the glycemia in type 1 diabetes compared to the healthy patient state is caused by the change of the insulin inflow in type 1 diabetes patients (which is entered not in the hepatic portal system, as in a case of the healthy patient, but in the peripheral systemic circulation).

It also shown that a stable blood glucose level in the basal state in type 1 diabetes can be achieved only in hepatic insulin resistance. Otherwise, in the type 1 diabetes patient the tendency to nocturnal and fasting hypoglycaemia should occur.

VIII. CONCLUSIONS

In this paper Patient-specific computer models that allow the simulating pathophysiological processes involved in type 1 diabetes mellitus are described. On the basis of theoretical analysis presented in [5] the Patient specific models of glycemia for distinct three cases: health

condition, the hepatic insulin-resistance and hepatic insulin-sensitivity in patients with diabetes are realized. These models can explain the predisposal of type 1 diabetes mellitus patients to diabetic retinopathy and nephropathy because eyes and kidney are
the insulin-independent tissues.

Modeling is performed using both the 2D and 3D Visual Membrane Petri Nets parallel software applications. It is shows that 2D and 3D VMPN open up new perspectives for modeling complex biological membrane systems and for development Patient specific models.

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