PATIENT-SPECIFIC COMPUTER MODELLING USING 2D AND 3D VISUAL MEMBRANE PETRI NETS

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Autorii propun un model computaţional pacient-specific care permite simularea unor procese fiziologice implicate în diabetul zaharat tip I. Modelarea se face cu ajutorul aplicaţiilor paralele 2D şi 3D Visual Membrane Petri Nets elaborate în baza conceptului de P sisteme şi a teoriei de Reţele Petri.

I. Introduction

We propose an integrated computational model for systemic investigation of the relevant aspects of compensatory physiological mechanisms, which evolve in the cardiovascular system and vital organs (brain, heart, gastrointestinal system, liver, kidneys, lungs) as well as peripheral blood circulation. This model allows to calculate the glycemia level in different parts of the human cardiovascular system (systemic circulation, pulmonary circulation, heart, coronary circulation).

Within the framework of our project we develop a new class of object-oriented, parallel and distributed software, namely 2D and 3D Visual Membrane Petri Nets (3D VMPN), applying the concept of P Systems ([1] Păun Gh.) and the Petri Nets theory [2,3]. We combine different fundamental characteristics into a single system for modelling of behavioural properties of the 3D membrane systems models and their visual interactive discrete-continuous simulation with emphasis on the relationship between spatial organization, shape and function.

This application represents a new stage in evolution of the Membrane Petri Nets concept proposed by our team [4,5]. At the beginning 2D Membrane Petri Nets software were elaborated [5]. Now our team has elaborated a novel application with 3D membranes which offers graphical representation of human body and of human organs. For spatial discrete-continuous performance simulation of multilevel biological systems there are 2 types of membranes: static and dynamic (for example, heartbeats are modeled with dynamic membranes).

The both of 2D and 3D VMPN accept the discrete-continuous place capacity, real values for continuous place marking and dynamic priority, marked-depended guard functions, arc cardinalities and firing rates. The continuous transitions of the net are fired with speeds that are piecewise constants or marked-dependent variable.

The parallel tool permits the description and visual simulation of adaptive, hierarchical, multilevel, spatial-temporal membrane models with 3D dynamic membranes, to capture the structural-functional hierarchical organization of complex multi-scale systems, which modify in run-time their own structure and parameters.

We've been developing a solution using MPI technology to simulate large-scale 3D membrane Petri net models. The 2D and 3D VMPN can run on Moldova State University cluster of computers (ROCKS). The aim of the project is to integrate in our patient-specific computer models the medical and informational concepts to offer a support both for doctors in the process of forecast and diagnosis of diseases, and for patients.

II. Parallel 3D VMPN Tool

In the following, we describe the 3D Visual Membrane Petri Nets parallel software tool for visual representation, formalization and simulation of patient-specific models. 3D VMPN is a window-based, object-oriented parallel software tool, in which elements typical both of generalized Petri net models (discrete-continuous places, transitions, arcs, etc.) and membrane systems are manipulated under the assistance of basic syntactical rules that prevent the construction of incorrect models.

Visual simulation is very useful during the early stages of the construction of the model since it represents a powerful tool for its debugging. Moreover, the animation of correct simulation model may provide important

insights on the behavior of actual systems. The dynamic graphical facilities are used to visualize the movement of the tokens (fluid), to provide snapshots of the model, and to represent the membrane system evolution.

The simulation is performed in 3D VMPN by first constructing the model on the screen of a graphical workstation (Client Level) using the facilities provided by the Graphical User Interface (GUI). Once the simulation model has been specified, a debugging phase must take place to ensure that it is first syntactically and then semantically correct.

The 3D VMPN application consists of 3 levels (Fig. 1):

- «Client Level» – .NET 4.0 WPF application for OS Windows. This application allows creating 3D Membrane Petri Nets models, simulating them (using native or parallel algorithm) and analyzing obtained data.

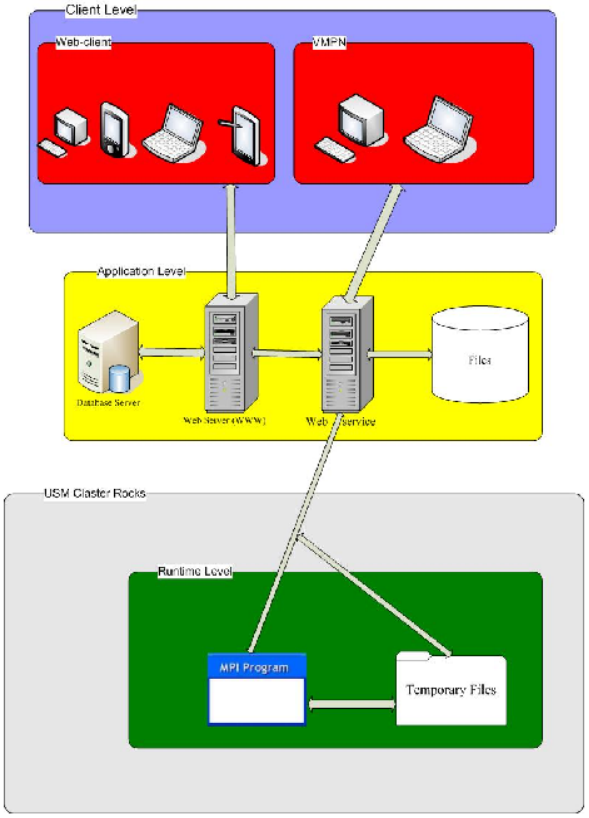

Figure 1. Three-level architecture: Client Level, Intermediate Level, Parallel Simulation Level.

- «Intermediate Level» – represents a Web-service and consists of two layers, which allow to connect to cluster and send/receive files using the proper protocols.
- «Parallel Simulation Level» – parallel program using MPI-technology which retrieves special files from client and runs the simulation of the model. After simulation the MPI-program saves file with simulation results.

The Web-Client of VMPN is the front-end program that makes user can work on a computer cluster with a friendly and easily understood interface (Fig. 2). This Web-Client is designed for clinicists. There are two main parts of Web-Client we developed for composing Web-Client of 3D VMPN, one is the management part, and another is the simulation part. In management part, doctor can input related data after inspecting a patient, Web-Client will store those data in a database (in our project, we use MySQL as database). After the completion of a series of examinations, clinicist can use Web-Client to do simulation in order to obtain a preview of the growth of diseases.

So, the client application is a WPF application developed for creating Membrane Petri Nets models, simulating and analyzing received data after simulation. It has an algorithm of simulation and allows users to run the simulation even if the cluster is not available. During the simulation process the user can watch animation

of transformations and interactions of some objects. He can interact with camera and move between membranes (or other Petri Nets objects) to watch what's happening inside of them. He can visualize how Petri Nets objects communicate or transfer data with each other.

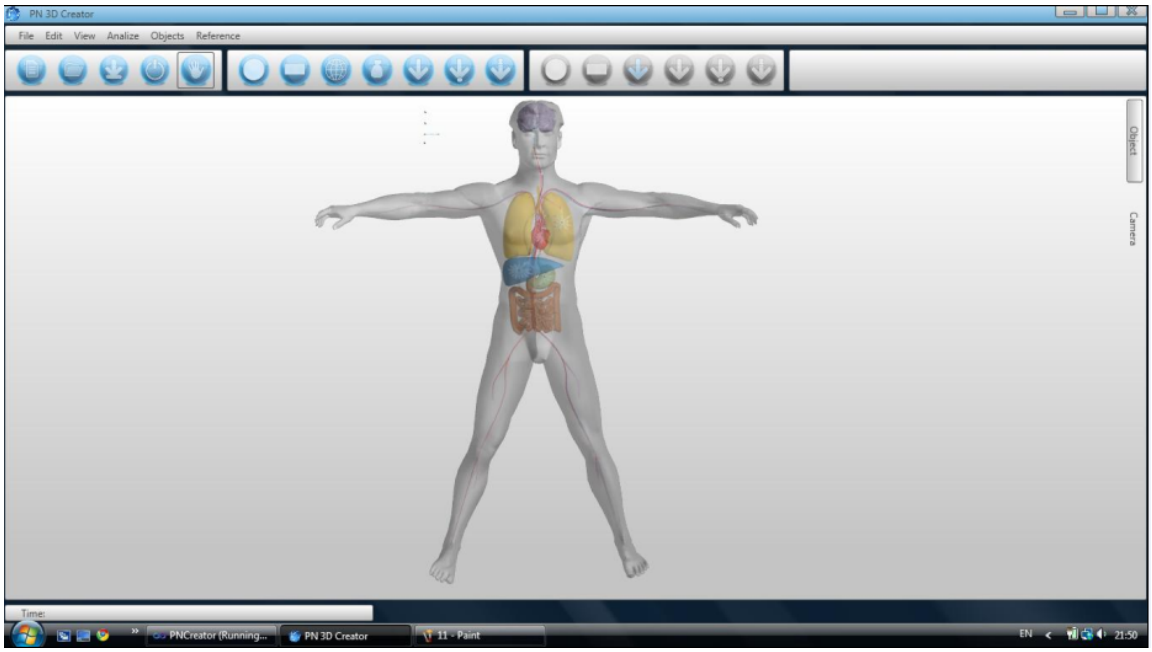

Figure 2. Representation of a window of the 3D VMPN software.

The area of creation and editing of a model is the main and the biggest part of the client. The toolbar contains essential functions of manipulation of the model. Likewise the toolbar has user controls which represent Discrete, Membrane and Continuous Petri Nets objects. It helps users to have a direct access to all available objects of Petri Nets for fast modeling process. All Petri Nets objects are transformable. This means that you can move, scale and rotate them. When a model was built you can simulate it. There are two options of simulation: 1) With animation – it means that user can watch simulation process step by step, including:

Changing behavior of each object; Changing size and form of some objects (for example, dynamic membrane visually can simulate the work of the heart, e.g. hearbeats). Visual animation of transferring some data between Petri Nets objects. 2) Without animation – it means that user cannot watch simulation process and he receives only results of the simulation. Therefore the user must set the number of simulation steps (simulation time). There is a possibility to simulate a model on a local machine or on a cluster (server). Users just need to set hostname, username and password. There are some situations when a property of the Petri Nets object depends of the properties of other Membrane Petri Nets objects and mathematical functions.

III. Patient-specific Computational Model

Our 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 [6,9]. The most important criteria both for diagnosing of diabetes and effectiveness of treatment is glycemia level in different parts of the cardiovascular system. In recent years were made a lot of experimental data related to glucose metabolism in different parts of the circulation [7,8]. We propose a 3D VMPN model of circulatory topography of glycemia level in different parts of the circulation on the basis of a theoretical analysis presented in [9]. Our model reflects different glucose concentrations (on 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.

At the beginning, a vascular topography model of glucose level in blood circulation was realized in the 2D Visual Membrane Petri Nets application (Fig. 3).

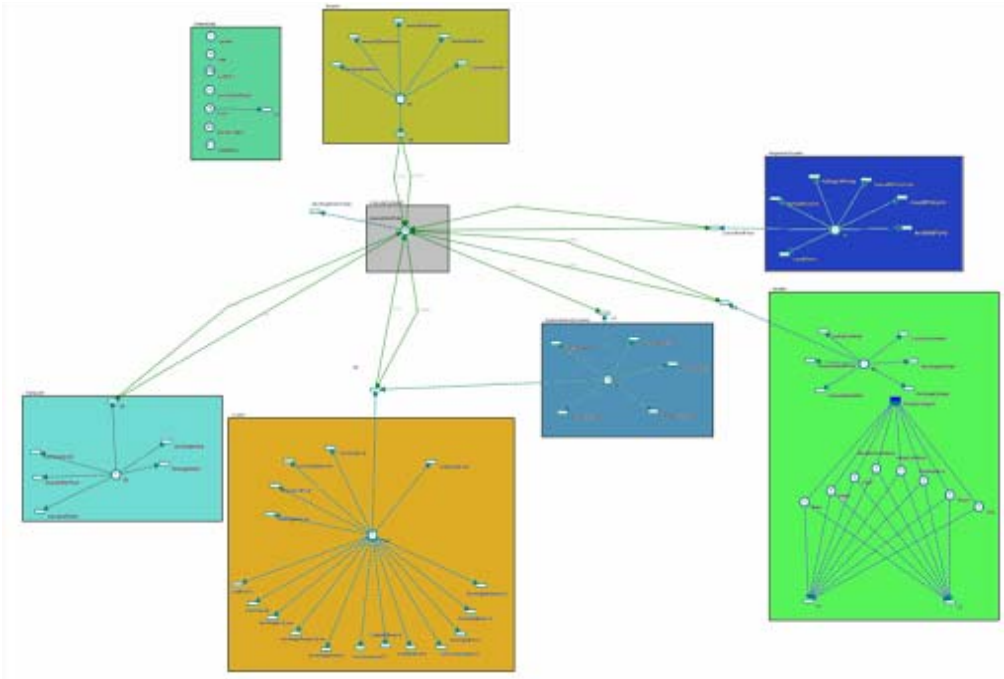

Figure 3. Representation of a vascular topography model of glucose level in blood circulation realized in the 2D Visual Membrane Petri Nets software application.

The same model was realized in the 3D Visual Membrane Petri Nets parallel software application. Screenshots are shown in Fig. 2 and Fig. 4.

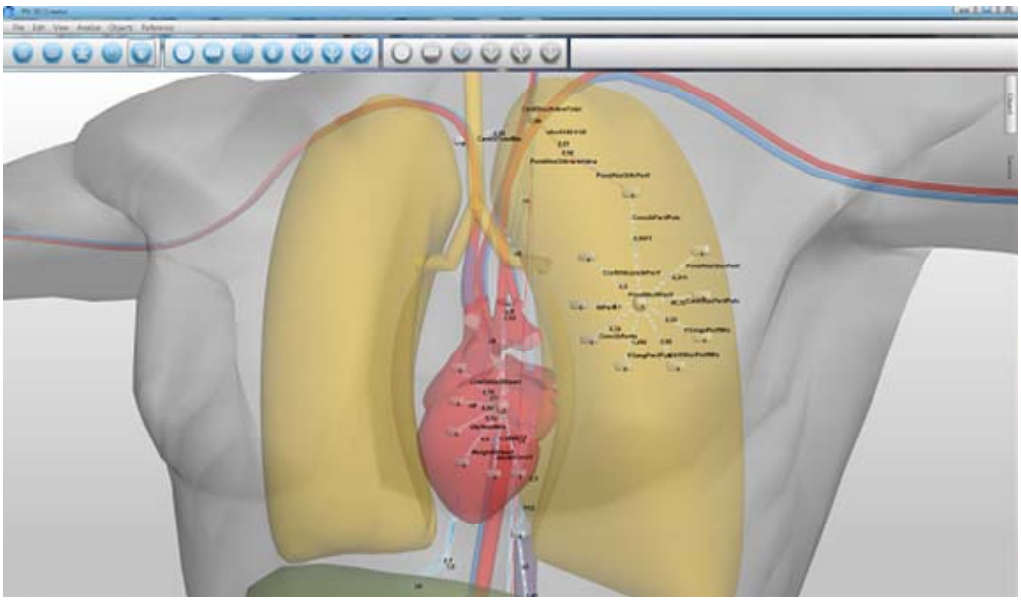

Figure 4. Representation of a part of the 3D Visual Membrane Petri Nets model of circulatory topography of glycemia (a part of the patient-specific model).

IV. Simulation Results

Normal level of glycemia in veins and early stages of pathophysiological processes (for example, hyper- and hypo- glycemia, blood levels of insulin hormon, cardiac cycles etc.) involved in the development of type 1 diabetes mellitus are modelled. Changes of glycemia level in insulin-dependent and insulin-independent tissuies in the case both of hepatic insulin-resistance and hepatic insulin-sensitivity are demonstrated through simulation.

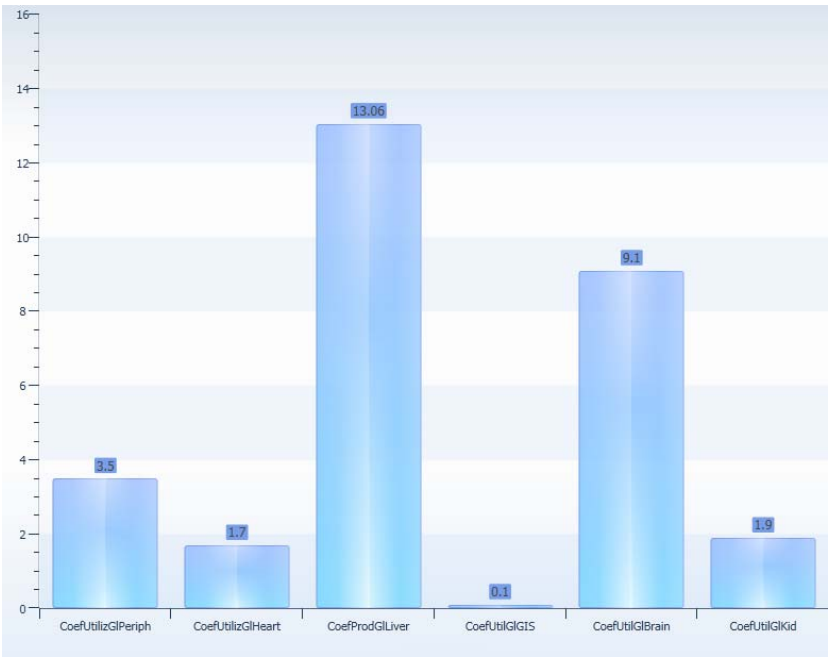

Figure 5. Glucose utilization/production coefficient in target organs/tissues: GIS, brain, kidney, periphery, heart and liver, respectively (*health condition*).

In Fig. 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).

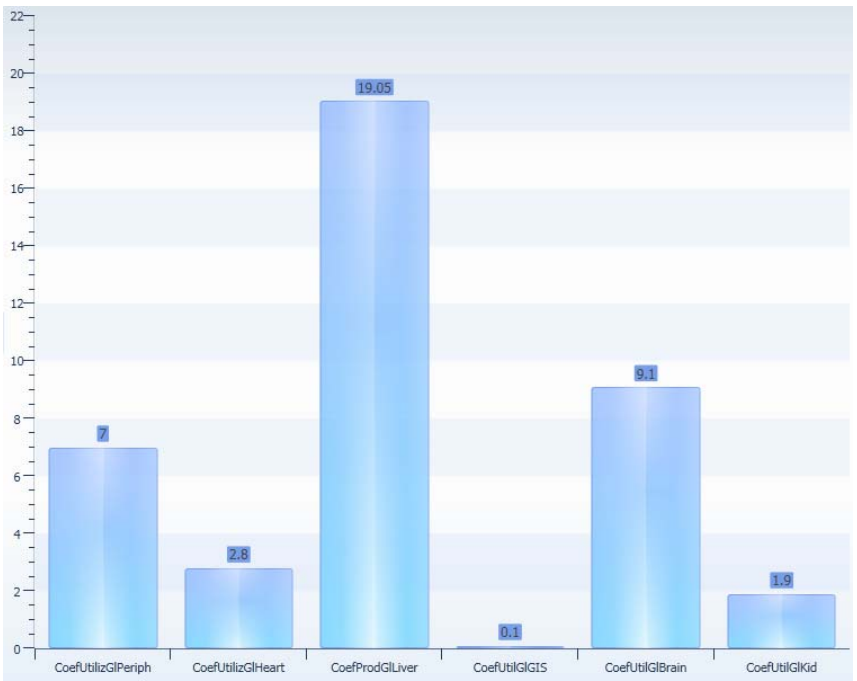

Figure 6. Glucose utilization/production coefficients in target organs/tissues (*hepatic insulin-resistance*).

In Fig. 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 type 1 diabetes (basal level) in blood vessels (blood insulin level – 45 μmol/l).

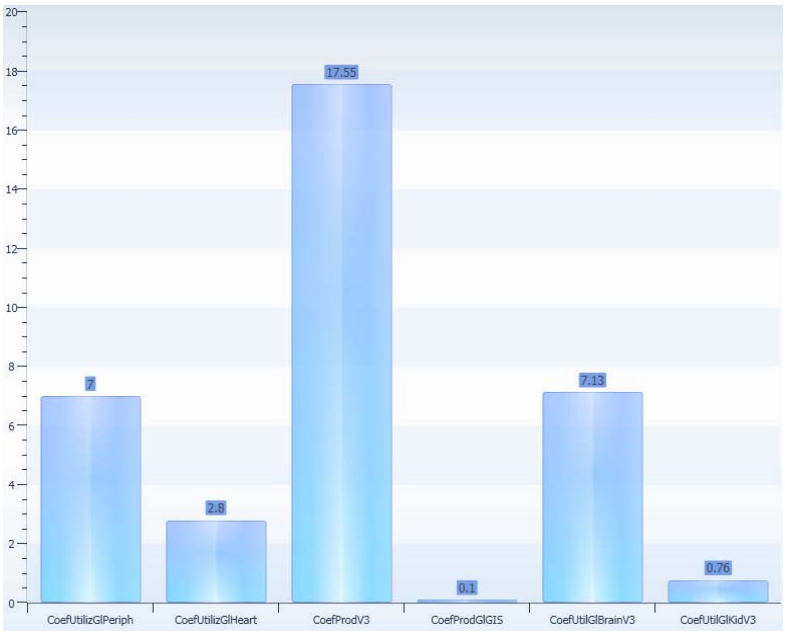

Figure 7. Glucose utilization/production coefficients in target organs/tissues (*hepatic insulin- sensitivity* (10%) in patients with type 1 diabetes) (basal level).

Fig.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 type 1 diabetes (basal level) in blood vessels (blood insulin level – 45 μmol/l).

It was shown that a stable basal glycemia level in type 1 diabetes mellitus could be reached only in case of hepatic insulin-resistance (high level of hepatic glucose production coefficient).

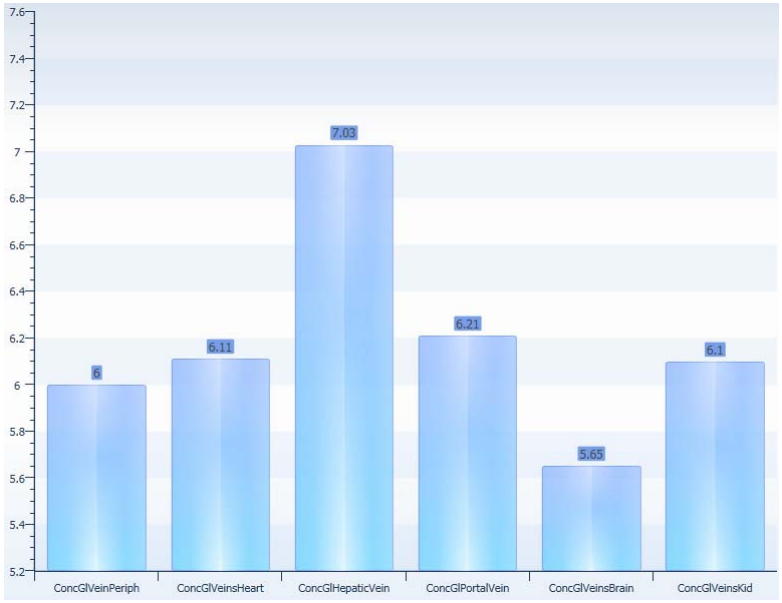

Figure 8. Glucose concentration level in veins (*health condition*) in target organs/tissues: periphery (6 mmol/l), heart (6.11 mmol/l), liver (7.03 mmol/l), portal vein (6.21 mmol/l), brain (5.65 mmol/l), and kidney (6.1 mmol/l).

Different levels of glucose concentration in veins in target organs/tissues are represented above (health condition). The simulation results presented in the following diagrams can explain the predisposal of type 1 diabetes mellitus patients to diabetic retinopathy and nephropathy because eyes and kidney are the insulin-independent tissues.

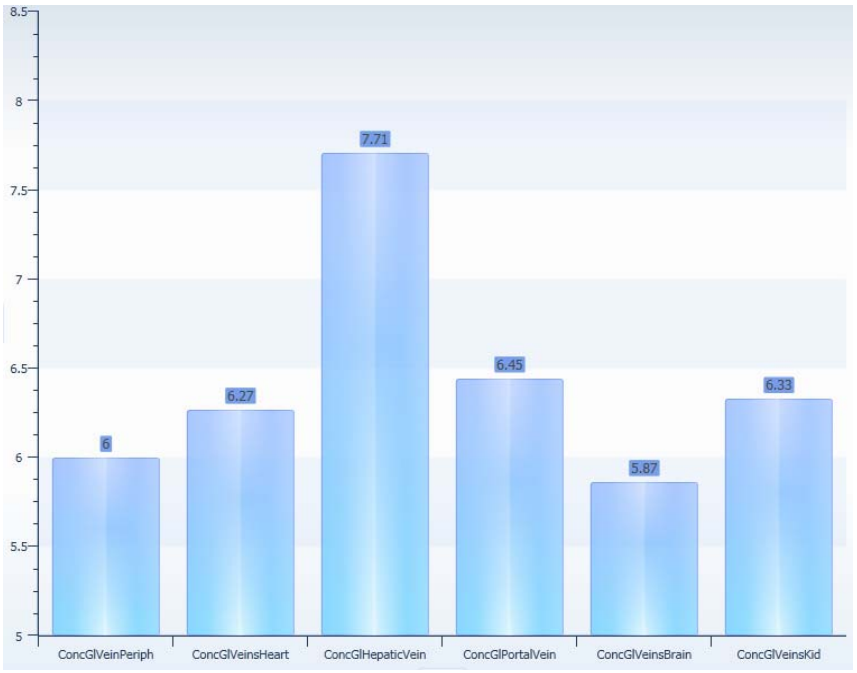

Figure 9. Glucose concentration level in veins (*hepatic insulin-resistance*) in target organs/tissues: periphery (6 mmol/l), heart (6.27 mmol/l), liver (7.71 mmol/l), portal vein (6.44 mmol/l), brain (5.9 mmol/l), and kidney (6.33 mmol/l).

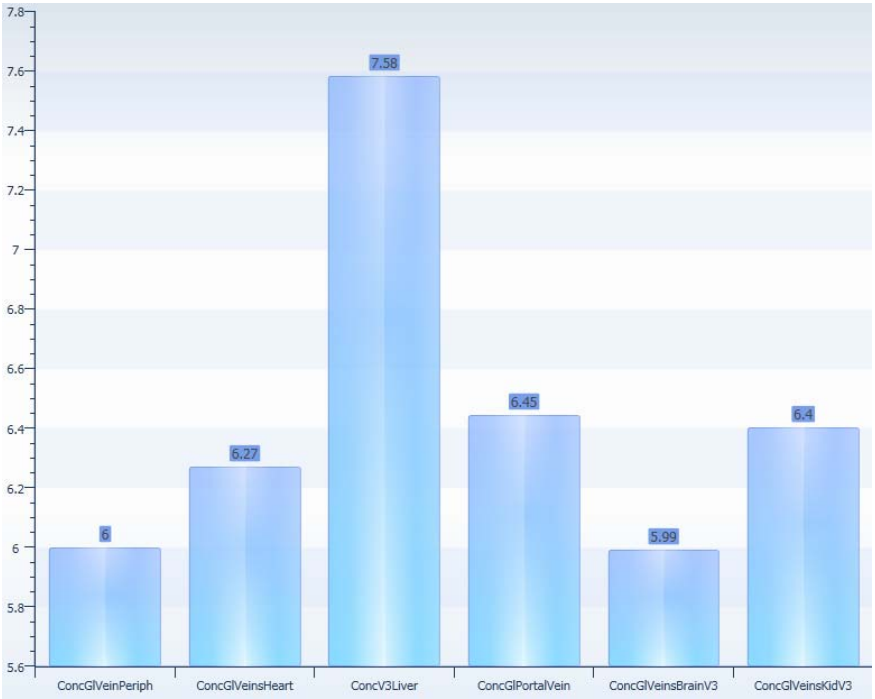

Figure 10. Glycemia level in veins (*hepatic insulin- sensitivity*) in target organs/tissues: periphery (6 mmol/l), heart (6.27 mmol/l), liver (7.58 mmol/l), portal vein (6.44 mmol/l), brain (5.99 mmol/l), and kidney (6.4 mmol/l).

It is shown in Fig. 8-10 that in case of stable basal glycemia level in type 1 diabetes mellitus the glucose concentrations in veins elevate in insulin-independent tissues (brain, kidney) even when glycemia level is normal in clinically useful peripheral circulation (6 mmol/l). The model of circulatory topography of glycemia can explain the predisposal of type 1 diabetes mellitus patients to diabetic retinopathy and nephropathy.

Conclusions

In this paper a patient-specific computer model that allows to simulate pathophysiological processes involved in type I diabetes mellitus is described. On the basis of theoretical analysis presented in [9] the model of circulatory topography of glycemia for distinct three cases: health condition, the hepatic insulin-resistance and hepatic insulin-sensitivity in patients with type 1 diabetes is realized. This model 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 the 3D Visual Membrane Petri Nets parallel software application. In the structure of the 3D VMPN software tool the membrane structure, which consists of 3D membranes representing human body and organs, is added as a basic component. Petri Nets with 3D membrane structures open up new perspectives for modeling biological membrane systems.

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