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Integrované modely fyziologických systémů jako teoretický podklad pro lékařské výukové simulátory

Integrated models of physiological systems as a theoretical foundation for medical training simulators

Summary

Medical simulators are of high importance for training in the medical decision-making procedure, making it possible to train the medical decision-making procedure in virtual reality. User interfaces of medical simulators need not consist only in a computer screen. Their role can also be assumed by a computer-controlled patient figure. The core of the simulators is a complex model of physiological regulations of the human body, which incorporates models not only of individual physiological subsystems, but also their connections to form a more complex unit. Recently, medical simulators have also become a marketable commercial article. The detailed structure of models used in commercial simulators (system of equations and appropriate parameter values) is usually not published and becomes a carefully guarded technological know-how. However, open-source models of integrated physiological systems also exist. Our contribution to the freely distributable databases of physiological system models is the free library PHYSIOLIBRARY designed for the Simulink environment (http://physiome.cz/simchips). Besides others, this library also contains the source code of interconnected physiological systems, which was used as the resource for our educational simulator “Golem“. The model of Coleman et al. “Quantitative Human Physiology“, now renamed to “Hummod“ (http://hummod.org), implemented using almost three thousand XML files, is one of the most extensive open-source models of interconnected physiological systems. Recent development of simulation environments brought new possibilities of more efficient development of extensive simulation models using the so called acausal modelling tools. The simulation language Modelica is one of such tools. Our implementation of the model “Hummod“ in Modelica introduced a much more transparent and intelligible description of the modelled physiological relationships. We have also unveiled several errors in the original model of the American authors, and we modified and expanded the model predominantly in the field of modelling the acid-base homeostasis of the environment. Our version of the model – “Hummod-Golem Edition“ (http://physiome.cz/hummod) incorporates connected physiological systems (respiratory, circulatory, renal, blood gas transfer, volume, ionic and acid-base homeostases, energy metabolism, and relevant neurohumoral regulation mechanisms). It allows for modelling a number of pathological conditions and corresponding therapeutic interventions. The model provides a theoretic foundation for educational simulators, particularly for the medical trainer “eGolem“, designed for medical teaching of acute medicine. Our technology of web simulator design described in more detail in the habilitation thesis is used in the implementation process of web simulators.

Souhrn

Pro výuku lékařského rozhodování mají velký význam lékařské výukové simulátory, umožňující procvičovat lékařské rozhodování ve virtuální realitě. Uživatelským rozhraním lékařských výukových simulátorů nemusí být jen obrazovka počítače. Může jím být i počítačem řízená figurína pacienta. Jádrem výukových simulátorů je komplexní model fyziologických regulací lidského organismu zahrnující modely nejen jednotlivých fyziologických subsystémů, ale i jejich propojení do komplexnějšího celku. Lékařské simulátory se v poslední době staly i žádaným komerčním artiklem. Podrobná struktura v komerčních simulátorech použitých modelů (soustava rovnic a příslušné hodnoty parametrů) obvykle není zveřejňována a stává se pečlivě chráněným technologickým know-how. Existují také ale i open source modely integrovaných fyziologických systémů. Naším příspěvkem do volně šířených databází modelů fyziologických systémů je volně přístupná knihovna PHYSIOLIBRARY vytvořená pro prostředí jazyka Simulink (http://physiome.cz/simchips). Tato knihovna mimo jiné obsahuje též zdrojový kód modelu propojených fyziologických systémů, který byl podkladem pro náš výukový simulátor „Golem“. Jedním z nejrozsáhlejších open-source modelů propojených fyziologických systémů je model Colemana a spol. „Quantitative Human Physiology“, nyní přejmenovaný na „Hummod“ (http://hummod.org), který je implementovaný pomocí téměř tří tisíc XML souborů. Nedávný vývoj simulačních prostředí přinesl nové možnosti pro efektivnější vývoj rozsáhlých simulačních modelů s využitím tzv. akauzálních modelovacích nástrojů. Jedním z těchto nástrojů je simulační jazyk Modelica. Naše implementace modelu „Hummod“ v jazyce Modelica přinesla mnohem průzračnější a srozumitelnější popis modelovaných fyziologických vztahů. Odhalili jsme také několik chyb v původním modelu amerických autorů, model jsme modifikovali a rozšířili zejména v oblasti modelování acidobazické homeostázy prostředí. Naše verze modelu - „Hummod-Golem Edition“ (http://physiome.cz/hummod) zahrnuje propojené fyziologické systémy (respirace, oběhu, ledvin, přenosu krevních plynů, objemové, iontové a acidobazické homeostázy, energetický metabolismus a příslušné neurohumorální regulační mechanismy). Umožňuje modelovat řadu patologických stavů a příslušných terapeutických zásahů. Je teoretickým podkladem pro výukové simulátory, zejména pro vyvíjený lékařský výukový trenažér „eGolem“, určený pro lékařskou výuku akutní medicíny. Při implementaci webových simulátorů využíváme naši technologii tvorby webových simulátorů, která je podrobněji popsána v habilitační práci.

Klíčová slova:

Modelica, modelování, fyziologické systémy, lékařské simulátory, Simulink, výuka

Keywords:

Modelica, modeling, physiological systems, medical simulators, Simulink, teaching

Contents

1. Schola Ludus for the 21st Century

“Tell me, I’ll forget, show me and I may remember; involve me and I’ll understand“ – this ancient Chinese wisdom is also confirmed by modern learning methods, sometimes called “learning-by-doing“, where simulation plays are widely applied. Simulation plays make it possible to test the behaviour of the simulated object without any risk – for example, try to land with a virtual airplane or, as is the case of medical simulators, treat a virtual patient or test the behaviour of individual physiological subsystems.

The connection of the Internet and interactive multimedial environment with simulation models provides quite new pedagogical opportunities, particularly when it comes to explaining complex interconnected relationships, active exercising of practical skills, and verifying theoretic knowledge. The old credo of John Amos Comenius “Schola Ludus“ – i.e. “school as a play“ [12] pioneered by this European pedagogue as early as in the 17th century finds its application in the incorporation of multimedial educational plays in training courses.

Simulation plays for the teaching of medicine are the core of the offer of numerous commercial companies. Besides commercial simulators, ***freely available*** educational ***simulators of individual physiological subsystems*** can also be found on the Internet. For example, the simulator ECGsim (**http://www.ecgsim.org/**) can be used to study the formation and spreading of electric potential in heart ventricles, and to study the mechanism of ECG formation in the presence of various pathologies [75]. Pressure--circulatory curves in heart ventricles in the presence of various pathologies can be observed using the heart simulator of the Columbia University (http://www.columbia.edu/itc/hs/medical/heartsim) [4]. Simulators of anaesthesiological instruments of the University of Florida allow for administering anaesthesia to a virtual patient (http://vam.anest.ufl.edu/). Blood gas transfer and acid-base parameters are the topics of the simulator OSA (Oxygen Status Algorithm), designed both for teaching and for clinical practice [70] (http://www.siggaard-andersen.dk). Activities of a neuron and neural networks can be studied using the simulation programme NEURON of the Yale University (http://www.neuron.yale.edu) [5, 27]. The training simulator AIDA (http://www.2aida.net/) models a virtual diabetic patient and allows for observing the effect of dosage of various insulin types with any assigned food intake on glucose metabolism [57, 64]. The Internet-based ***Atlas of Physiology and Pathophysiology*** is one of the results of our efforts in this area. The Atlas has been conceived as a freely available multimedial educational aid that utilizes the visual way to explain, through the Internet and simulation models, the function of individual physiological systems, the causes and manifestations of their disorders – http://physiome.cz/atlas [42, 43, 48].

2. Medical training simulator

The interface of educational simulators need not be represented only by a computer screen. The development of haptic scanning technology and of virtual reality imaging has brought a new class of simulators designed for training practical performance of some medical tasks (cardio-pulmonary resuscitation, catheterization, endoscopy, patient intubation, etc.) on a patient figure. However, also hardware trainers have been offered in increasing levels, designed at the same time also for training the medical decision procedure [23, 58]. For example, the Norwegian company Laerdal (http://www.laerdal.com/) manufactures a set of robotized simulators including the simulator SimBaby, used with a success as a medical trainer for newborn and infant care [68]. Laerdal trainers have proved to be useful not only in the training of doctors, but also in education of nurses [6]. The American company METI (http://www.meti.com) is another successful manufacturer whose robotized trainers provide a highly efficient (although costly) educational aid for the training of anaesthesiologists and medical care teams, particularly in the field of acute conditions medicine [16,69].

Similarly as air trainers, medical trainers allow for implementing a quite new way of teaching where the student may practice diagnostic and therapeutic tasks in virtual reality, associated with no risk for the patient. Similarly as airline pilot simulators, the trainer itself is controlled from within the operator site where from the teacher may control the simulated patient and choose from various scenarios of simulated diseases. All actions of students are monitored and the simulator provides grounds for later debriefing of the diagnostic and therapeutic procedure of the students [8].

As noted by many authors in recent times in particular, teaching with a simulator imposes fairly higher demands on the teacher than classical teaching methods. However, provided that the simulator is used correctly, the pedagogical effect is very marked, especially in areas where fast and correct decision-making is very important, for example, in acute conditions medicine and in anaesthesiology [3,13,29,30,61,66,78].

Similarly as the theoretic foundation of an air simulator is based on an airplane model, medical simulators are based on a sufficiently truthful model of physiological systems in the human body. Its detailed structure (system of equations and parameter values)) is usually not published for commercial trainers and becomes a carefully guarded technological know-how.

3. Integrative physiology

Models used as the theoretic foundation of medical trainers include ***mathematical models not only of individual physiological subsystems, but also their interconnections, thus forming a more complex unit***. The field of physiological research dealing with the study of interconnected physiological subsystems of the body seeks to describe the physical reality and explain the results of experimental research, as well as “integrative physiology“ seeks to create a formalized description of the interconnected physiological regulations and explain their function in a healthy human and also for conditions of various diseases.

Formalized description of the circulatory regulation in connection with other physiological subsystems was one of the first extensive mathematical descriptions of physiological functions of the interconnected subsystems of the body; this description was published in 1972 by A. C. Guyton with two other authors [19]. Right at first glance, the article went absolutely beyond the scope of the habitual form of physiological articles of that time. Its essential part was formed by an extensive diagram pasted in as an appendix, remotely resembling a drawing of some electronic device. However, instead of electronic components, the diagram showed interconnected computational blocks (multipliers, dividers, summators, integrators, functional blocks) that symbolized mathematical operations performed with physiological variables. Instead writing a system of mathematical equations, graphic representation of mathematical relationships was used in the article. The whole diagram thus represented a formalized description of physiological relationships using a graphically expressed mathematical model.

The authors applied this way, quite new then, of using graphically expressed mathematical symbols to describe physiological regulation of the circulatory system and its wider physiological contexts and connections to other subsystems of the body. The comments and reasons for the formulations of the mathematical relationships were very brief. Later, in 1973 and subsequently also in 1975, monographs [20] were published providing a more detailed explanation of a number of the approaches applied.

Guyton's graphic notation of the formalized description of physiological relationships was soon adopted also by other authors – for example, Ikeda et al. [28] in Japan or the research group of Amosov in Kiev [2]. However, graphic notation of a mathematical model using a network of connected blocks was a mere image representation at that time – the Guyton's model as well as its additional modifications (similarly as models of other authors who adopted the expression notation of Guyton) were implemented in Fortran and later in C++ language. Guyton and his collaborators and students kept developing the model continuously [63, 7]. The Guyton's model was an inspiration as well as a resource for designing complicated complex models of physiological regulations used to explain causal chains of reactions in the body to various stimuli, and also to understand the development of pathological conditions. Besides others, a modified Guyton's model has become one of the foundations for an extensive model of physiological functions in the NASA programme "Digital Astronauts" [79].

4. Large scale models for educational simulators

As early as at the beginning of the 70ies, Guyton was aware of the large potential of using models as independent educational aids, and he developed an effort to apply them in education within the realm of the then capacities of computer technology. He used his graphic diagram in the classes to explain basic relationships among individual physiological subsystems. A model implemented in Fortran on a digital computer was used concurrently to observe their behaviour in the course of adaptation to various physiological and pathological stimuli. Later, in 1982, one of Guyton's collaborators, Thomas Coleman created the model "***Human***" designed predominantly for educational purposes [9]. The model allowed for simulating a number of pathological conditions (cardiac and renal failure, hemorrhagic shock, etc.), and the impact of some therapeutic interventions (infusion therapy, effect of some drugs, blood transfusion, artificial pulmonary ventilation, dialysis, etc.). Recently, Meyers and Doherty made the original Coleman's educational model Human implemented in Java available on the web [62].

At the time when the Guyton's model was published, in the first half of the 70ies, application of computer models in medical education was the privilege of only several universities, and it depended especially on technical equipment and enthusiasm of the personnel of the given faculties. The Department of Biocybernetics of the Institute of Physiology, Faculty of General Medicine, Charles University in Prague was one of such pioneer departments at the Charles University, where as part of their training in physiology the students became acquainted with basic terms of system theory, general principles of regulator circuits and their applications to physiological regulation [80, 81]. The students worked with models implemented on the analogue computers MEDA and later, as allowed by the technical equipment of the department, also on digital computer terminals [82].

In the 80ies, we also embarked on the development of our own extensive model of mutually connected physiological regulations focused predominantly on modelling the disorders of homeostasis of the inner environment. The model of acid-base equilibrium and of blood gas transfer [31] was expanded to a complex model of the inner environment hemostasis [18, 39, 45, 46, 47]. Besides others, the created model was a part of a wider project of using mathematical models of the human body in the Soviet cosmic research [77], similar to the American NASA project "Digital Astronauts" [79]. Some subsystems of the model found their practical applications also in calculations of some clinical-physiological functions by means of identifying the model to measured clinical data [44].

In the middle of the 80ies, we also attempted at using our complex model of the inner environment in classes. Communication with the model running on remote hardware ran through an alphanumeric terminal. Interactivity was therefore somewhat cumbersome, only numeric outputs were used, and pseudographs created from character sets replaced any graphic output. In the end, the pedagogical effect therefore did not correspond to the effort that we devoted to its implementation. We returned to the issue of educational simulators as late as in the second half of the 90ies when the progress of information technologies made it possible to create educational simulators applicable in practical teaching of medicine.

5. Models and "simulation chips" in Simulink networks

Today, designing simulation models is facilitated by specialized software environments. Matlab / Simulink of the company Mathworks is one of them. It includes the graphic simulation language Simulink that can be used to set up a simulation model from individual components using the mouse – thus a model of a kind of software-based simulation parts that are connected to form simulation networks. Simulink blocks highly resemble elements used by Guyton for his formalized expression of the physiological relationships. Their graphic shapes are the only difference.

Besides others, this similarity inspired us to resurrect the old classical Guyton's diagram and transform it into a functional simulation model [32]. We tried to preserve quite the same external appearance of the Simulink model as in the original graphic diagram – the layout, placement of wires, names of variables, and even block numbers are the same.

However, simulation-based visualization of the old diagram was not quite easy – there are namely errors in the original picture diagram! This is not a problem for a drawn picture, but if we try to liven it up in Simulink, the model collapses immediately as a whole. For a detailed description of the errors and their corrections see [33, 49].

It is of interest that the Guyton's diagram as a complex picture has been reprinted many times in various publications – recently, it appeared for example in [7.22, 76].

However, no one pointed out the errors before us, and no one took the trouble to remove them. No drawing programs existed yet at the time when this picture diagram was created – the picture was created as a complex drawing – and manual redrawing of the complex drawing was not easy. It is even possible that the model authors themselves ha no special desire to correct the errors – those who took the pains to analyze the model unveiled the graphic "misprints", while those who would only like to copy without thinking had no luck. After all, in their times the authors also distributed source codes of the programs of their model in Fortran – there was thus no need to program anything if only the model behaviour was to be tested. Our Simulink implementation of the (corrected) Guyton's model is available for download at http://www.physiome.cz/guyton. Our Simulink implementation of a much more complex version of the model of Guyton et al. from later years is available on this website, as well. At the same time, very detailed description is provided of all the used mathematical relationships, together with reasons for them.

However, the Guyton's diagram and the Simulink network designed based on the diagram are quite difficult to survey at first glance. In order to increase its clarity, it is advisable to hide the actual active elements of the Simulink calculation network (multipliers, dividers, integrators, summators, etc.) in individual subsystems implemented in Simulink as user blocks with appropriate inputs and outputs from the outside. The whole model then consists of interconnected blocks of individual subsystems where it can be seen clearly what variables are used to connect individual subsystems, while the algorithm of the actual simulation computation is hidden in the Simulink network within the blocks.

The blocks can be saved in libraries as user-defined subsystems. In the process of creating models, the blocks can be taken out from the library, connected and grouped in blocks of a higher hierarchic level as the case may be. Individual Simulink subsystems represent a kind of "simulation chips" hidden from the user by the structure of the simulation network, similarly as an electronic chip hides from the user the connection of individual transistors and other electronic elements. The user may thus be concerned only with the chip behaviour, and need not worry about the inner structure and algorithm of the computation. The "simulation chips" can be used for easier testing of the model behaviour, and especially for clearer expression of mutual dependencies among variables of the modelled system. The whole complex model can be shown as interconnected simulation chips, while it follows clearly from the structure of their connections what effects are considered in the model and how.

This approach provides important advantages in cooperation of multiple specializations – particularly in borderline fields, such as modelling biomedical systems. An experimental physiologist does not have to examine in detail what mathematical relationships are hidden "inside" the simulation chip; however, he/she will understand the model structure from the connections among individual simulation chips, and can verify the chip behaviour in an appropriate simulation-based visualization environment [40].

The Simulink blocks were used to create a ***library of physiological models called Physiolibrary***, which is freely available at: http://www.physiome.cz/simchips. The library also includes an extensive integrated model of physiological regulations that has been used as the foundation for our ***educational simulator Golem***. The model uses a hierarchic structure composed of individual nested and interconnected Simulink blocks [37].

6. Golem instead of the patient

Besides the model, additional considerable programming efforts were needed to design the educational simulator ***Golem***, which consisted in creating the user interface and connecting it to the verified model implemented on the background of the simulator [36].

The simulator "Golem" designed as open source at the end of the 90ies focused predominantly on the teaching of the pathophysiology of inner environment disorders [34, 35, 50-54]. It allowed for simulating especially mixed disorders of ionic, osmotic and acid-base equilibrium, disorders of blood gas transport, respiratory failure and renal failure. It also allowed for observing the effect of various infusion therapies.

The simulator has been used at our and some foreign medical faculties. It proved itself especially in the teaching of pathophysiology and clinical physiology. Thanks to the complexity of the physiological systems model on its background, the simulator could be used to demonstrate clearly ***how individual physiological subsystems are related with each other, and how these connections are manifested in individual pathophysiological conditions***.

From the pedagogical point of view, it proved to be highly advantageous to explain the physiological meaning of individual regulator circuits by means of ***disconnecting and reconnecting individual regulatory bonds***. Upon disconnecting regulatory bonds in the simulator, ***the response of individual physiological subsystems*** on changed values of some variables ***can be observed locally***, which themselves are regulated in the body, though. We have therefore introduced in Golem the ***possibility of "disconnecting regulation"*** of some regulated physiological variables, and their "switching to local input" [38]. Disconnection of the regulatory loops made it possible to limit the simulation to an individual physiological subsystem, and to examine its behaviour independent of the complex regulatory relationships within the whole body, and thus to observe the behaviour of individual physiological regulatory relationships separately, which contributed to better understanding of the physiological relationships. However, our experience as well as the experience of other departments with the deployment of complex models in teaching show that large and complicated models provide a considerable disadvantage from the didactic point of view due to their complex control [14, 56, 48]. Large amounts of input variable require that the user acquires a more profound understanding the very structure of the simulation model, as well as knowledge of what processes should be observed during the simulation of certain pathological conditions.

Pedagogical practical experience showed that simulation plays with simple aggregated models (enabling the user to observe only several variables) is sometimes a more suitable tool for explaining complex processes than an extensive and complicated educational simulator. It is advisable to proceed from simple to more complex things in the explanation, i.e. explain the basic principles at first using simple models, and only them pass on to more complex details and use simulation plays with more complex models.

It is suitable to use the models together with explaining their use – at best using interactive educational applications on the Internet. It is only the ***connection of the lectures with a simulation play*** that provides the possibility of utilizing all advantages of virtual reality to explain complex pathophysiological processes.

In order to join the potential of interactive multimedia and simulation models for the teaching of medicine, we have therefore designed the project of an Internet and computer-based ***Atlas of Physiology and Pathophysiology*** (http://physiome.cz/atlas), which combines interactive explanatory chapters and simulation plays with models of physiological systems. The user interface resembles animated pictures of the printed Atlas of Physiology [71] or Atlas of Pathophysiology [72]. However, unlike printed illustrations, the pictures that form the user interfaces of multimedial simulators and ***"live"*** and ***interactive*** – changes of ***variables of the simulation model*** are reflected in a ***change of the picture***. Thus conceived interactive illustrations can be used to implement simulation plays that help, better than a static picture or even a simple animation, to explain the dynamic relationships in physiological systems, and thus also help especially to understand the causal relationships in the development of various diseases. In the process of designing the atlases, we have stemmed from our web-based educational simulator design technology [41].

7. From Simulink to Modelica

Simulink is one of ***block-oriented simulation languages*** that allow for setting up computer-based models from individual blocks with defined inputs and outputs, where the blocks can be connected to form computational networks, and the computational networks can be grouped into block of a higher hierarchic level. Block-oriented simulation tools provide the advantage that they make it possible to structure the model clearly into connected, hierarchical components. The structure of a block-oriented description thus shows clearly how the values of individual variables are calculated in the model – i.e. what the computational algorithm is. The term ***causal modelling*** is thus used. However, the blocks cannot be connected to the network of relationships quite arbitrarily, unfortunately. Algebraic loops may not exist in the connected elements – i.e. cyclic structures where some input value introduced as an input to a computational block depends (through several intermediary elements) on the output value from this block in the same time step. The way of connecting the blocks reflects rather a ***computational procedure*** than the very structure of the modelled reality.

Recently, new, the so called ***"acausal"*** tools to create simulation models were developed. An essential innovation brought by acausal modelling tools is represented by the possibility of describing individual parts of the model directly ***as a system of equations and not as an algorithm to solve the equations***. The notation of the models is thus declarative (the structure and mathematical relationships are described, not the computational algorithm) – the notation is thus acausal.

Acausal modelling tools work with connected components that represent instances of classes where equations are defined directly. The components may be connected through special acausal connectors –an acausal connection actually means that individual variables in the equations of appropriate components are connected, and their connections define the systems of equations of the model.

Elementary elements of simulated reality may take the form of a very trivial notation of relationships among quantities. For example, resistance, capacitor or coil from the electrical physical domain or their hydraulic analogies (used e.g. for the circulatory system modelling) can be named as illustrative examples. A more complex computational system arises upon connecting such elementary elements in networks – systems of equations are obtained upon their mutual connections. An algorithm of their numerical solution written in Simulink may not be trivial (see e.g. more complex, the so called “RLC models“ of circulation or respiration implemented in our Simulink library Physiolibrary). However, there is no need to care about the way of solution in acausal simulation tools. It is the acausal tool itself that takes care of solving the obtained system of equations.

Modelica is a modern simulation language built directly on acausal notation of models [17, 74]. Unlike the block-oriented simulation environment Simulink, the structure of Modelica models shows much better the physical essence of the modelled reality (an appropriate compiler then takes care of the solving algorithm of the resulting system of algebraic differential equations). Models in Modelica are, compared to those in Simulink, clearer and self-documenting.

A simple example from the field of hemodynamics modelling can be used to illustrate this. In order to model the resistance of a blood vessel, we shall create a class and write the Ohm’s law equation in the class. A user-defined icon may be assigned to every class – for example, graphic representation of the vessel in the given case (see Fig. 3). In order to facilitate its interconnection with the surroundings, we shall add a connector to the class, which will be used for conductance values input in the case of resistance, and at the same time, we shall define acausal connectors at both ends of the vessel.

Acausal connector-based connection can be implemented using two types of quantities: One that represents flow – where the sum of flows at all connected nodes is null (because no material is accumulated at the bifurcation point of the nodes), and another whose value remains the same at all the connected nodes. The flow variable is blood flow for the component that models vascular resistance, while the nonflow variable is blood pressure. The pairs of connected flow and nonflow variables may differ for other components (such as the material flow as the flow variable, material concentration as the nonflow variable).

The so called elastic compartment (see Fig. 1) is used often in vascular dynamics modelling. The elastic compartment concept is based on the idea that if a vessel is filled with blood, the vascular pressure is determined only by the external pressure exerted on the vessel (“*ExternalPressure*”) up to a certain residual volume (“*V0*”); afterwards, the elastic and muscular fibres in the vessel start stretching and the vascular pressure rises proportionally to the difference of the vascular volume (“*Vol*”) and residual volume (“*V0*”).

An elastic vascular compartment can be imagined as an inflatable bag with one acausal connection connector (called perhaps the “*ReferencePoint*”) used for connecting the compartment to the surroundings. This connector provides us with two va-

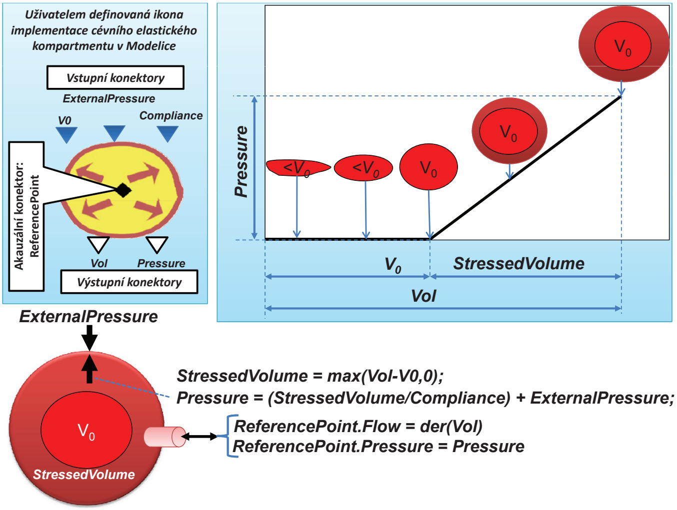

Figure 1: Concept of an elastic vascular compartment and its implementation in Modelica.

lues:

- Flow *”ReferencePoint.Flow“*;
- Pressure *”ReferencePoint.Pressure“*

Three signal inputs will enter the compartment from the outside:

- Basic fill “*V0*” – volume value from which, when achieved, external pressure will start rising during filling of the vessel, thus the external pressure of the outside surroundings exerted on the vessel *”ExternalPressure“*
- Compliance of the elastic compartment *”Compliance“* – besides others, its value depends on the tension of muscular fibres.

Two (causal) signal outputs will exit the compartment on the outside:

- Information on the momentary volume of the compartment *”Vol“*;
- Information on the pressure value within the compartment *”Pressure“*.

An icon used to display the elastic compartment can be designed in the programming environment, as well.

The program fragment that describes the behaviour of the elastic compartment is as follows in Modelica:

```
model VascularElacticBloodCompartment;
...
equation
        StressedVolume = max(Vol-V0,0);
        Pressure = (StressedVolume/Compliance) + ExternalPressure;
        der(Vol) =  ReferencePoint.Flow;
        ReferencePoint.Pressure = Pressure;
end VascularElacticBloodCompartment;
```

The first equation declares that the value of the elastically stressed volume “*StressedVolume*” will be calculated as the difference between the compartment volume “*Vol*” and the value of its basic fill “*V0*” (which is the input); furthermore, the equation says that the compartment volume value can never decrease to negative values. The second equation declares the relationship between the compartment pressure “*Pressure*”, the stressed volume value “*StressedVolume“,* compliance “*Compliance“*, and the external pressure “*ExternalPressure“*. The reader should be reminded once again that these are equations and not assignments. The equation could be written in Modelica also as follows:

Pressure – ExternalPressure= (StressedVolume/Compliance);

The third equation is a differential equation – volume derivation “*der(Vol)“* is equal to the flow “*Flow“* coming from the connector “*ReferencePoint“*. The last equation connects the compartment pressure value “*Pressure“* with the pressure value “*ReferencePoint.pressure“* connected with the surroundings by means of the acausal connector.

The value “*Pressure*” is a signal output from the compartment at the same time –

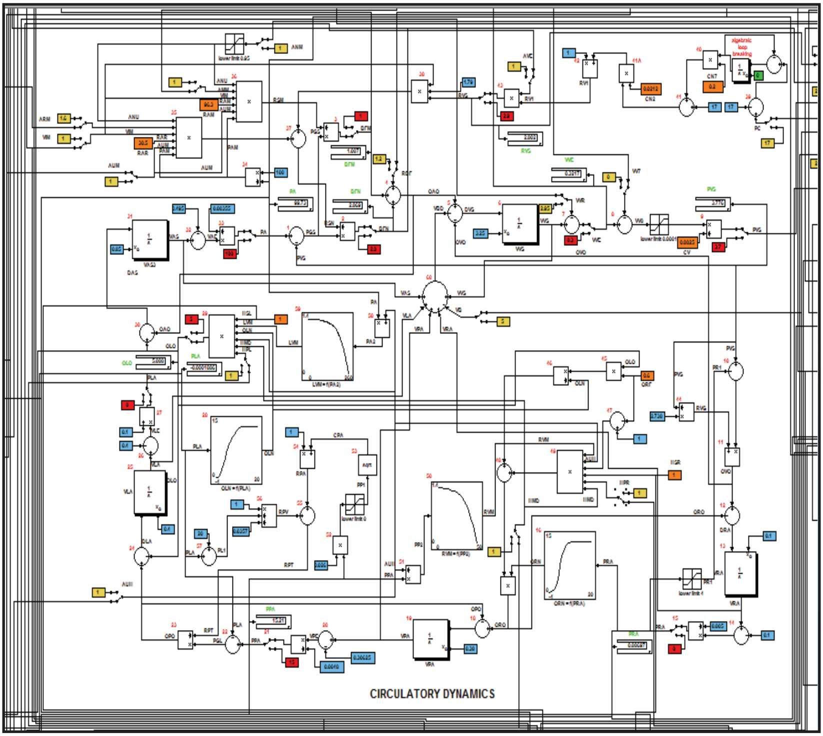

Figure 2: Circulatory dynamics – detailed structure of the central part of the Guyton’s model implemented in Simulink, which shows blood flows through aggregated parts of the circulatory system, and action of the heart as a pump.

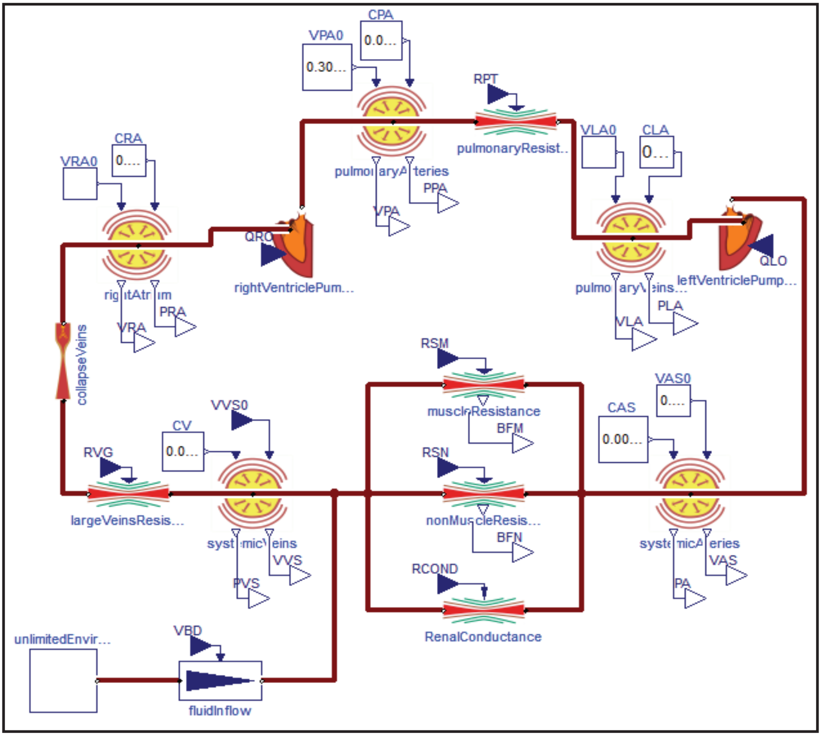

Figure 3: The same part of the model as in Figure 2, but implemented in Modelica. The model contains connected instances of two pumps (of the right and left heart ventricle), elastic vascular compartments, and resistances. Upon its comparison with Fig. 3, it can be seen that the model structure in Simulink corresponds rather to a computational algorithm, while the model structure in Modelica shows more of the structure itself of the modelled reality.

and being a signal, it can be brought to other blocks – but it is a causal output (signal) variable and its value cannot be affected by the element it is connected to. However, the situation is different in the case of connections from an acausal connector. Upon connecting an instance of the elastic compartment with other elements using an acausal connector, the four equations in the compartment become a part of the system of equations given by the appropriate connection, and variable values in the elastic compartment instance will depend on solving the thus created system of equations.

Until now, Modelica has been largely used in the industry. It facilitates modelling considerably, especially that of extensive and complex systems, which also include biomedical systems, though. Therefore we have opted for Modelica as the new implementation tool for the creation of educational simulator models, thus abandoning the development of models in the block-oriented environment Simulink/Matlab.

An advantage can be demonstrated for example by the comparison of implementation of the classical Guyton's model [19] in Simulink (Fig. 2) and in Modelica (Fig. 3).

The central part of the Guyton's model (Circulation dynamics) represents circulation modelling of blood pumped by the right and left heart ventricle. The Simulink model represents a complex computational network, complex at first glance. The Modelica implementation provides a clear view of the essence of the modelled reality – it consists of instances of two pumps (right and left ventricles), instances of elastic compartments, and resistances of individual parts of the vascular bed, interconnected through acausal connectors (that connect the flow and pressure in individual parts of the blood stream). The acausal connector of large veins is moreover connected to a controlled pump used to model blood formation or loss, infusions, and volume transfers from blood and interstitial liquid.

8. Hummod, Golem edition – model for the medical training simulator eGolem

Advantages of the acausal approach have been fully applied in the implementation of an extensive model of physiological regulations, which is used as the foundation of the medical training simulator ***eGolem*** in the process of preparation. The model structure stems predominantly from the structure of a model of American authors named ***Quantitative Human Physiology (QHP)***, recently renamed to ***Hummod***, [11, 24-26].

The large educational simulator ***Quantitative Circulatory Physiology (QCP)*** is the predecessor of this model [1], obtained upon further elaboration of the Coleman's model ***Human*** [9] and large models of the Guyton's working group. In order to support its use as an educational aid in medical teaching, the authors made the model freely available from the website of the University of Mississippi (http://physiology.umc.edu/themodelingworkshop/). The simulator ***QCP*** can be downloaded and installed on a Windows computer. It includes a high number of variables (several thousand). The simulator allows for changing the values of approx. 750 parameters that modify physiological functions. The values of these parameters can be saved in an external file or read from an external file, which enables the user to prepare a number of scenarios for various scenarios of the modelled pathological conditions. The authors have prepared many of the scenarios (as input files) for educational needs, and together with appropriate comments, they made them available for free download from the respective website. The simulator proved to be useful in the teaching practice [65].

The simulator ***Hummod*** with its more than 4000 variables apparently represents today the most extensive integrated model of physiological regulations. The model includes a menu branched abundantly, and it supports the simulation of numerous pathological conditions including the effect of any therapy.

Unlike the previous simulator QCP whose mathematical background is hidden from the user in the source code of the simulator written in C++, the simulator ***QHP/Hummod*** has taken a different way. Its authors decided to separate the simulator implementation and description of the model equations in order to make the model structure clear for a wider scientific community.

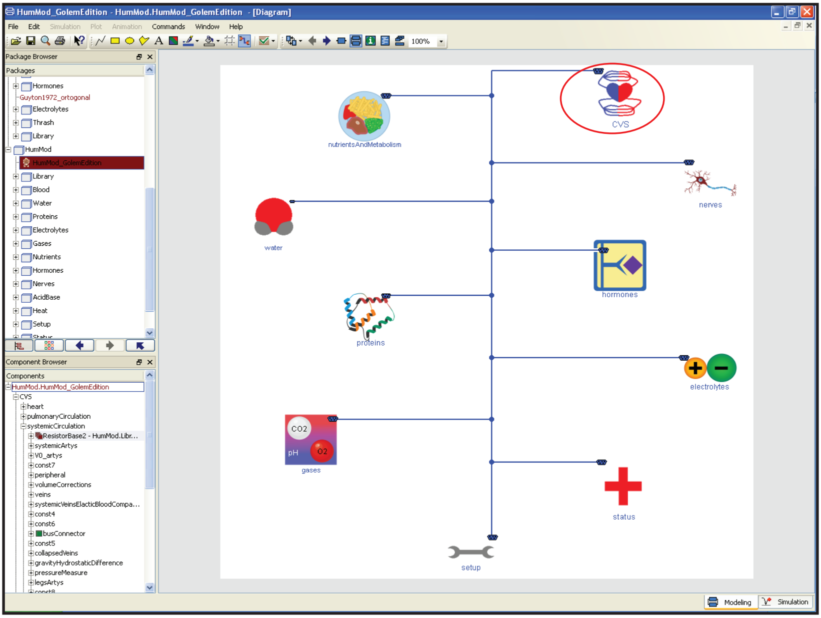

Figure 4: Structure of the model Hummod-Golem Edition. The model consists of the cardiovascular component (CVS), nutrition and metabolism component, water and osmotic homeostasis component, protein component, blood gas and acid-base homeostasis component, electrolyte homeostasis component, nervous regulation component, hormonal regulation component, the component of assessment of the patient's clinical condition, and the component of setting the initial status and modelled scenarios. All the components are connected through bus connectors.

As early as in 1985, the main architect of this model, Thomas Coleman therefore elaborated a special language for writing the model structure as well as definitions of the user interface elements of the simulator. The language is based on a modified XML notation. The model is then written using XML files, which are compiled subsequently by a special compiler (DESolver) into executable code of the simulator.

The model ***Hummod*** is distributed in its source form as open source (the model and the simulator are available to the public at the website http://hummod.org). Its structure is written in a special XML language and incorporates 3235 files located in 1367 directories. Thanks to this fact, the model equations and their relationships are comprehensible with difficulty, and many research teams dealing with the development of medical simulators therefore prefer to use older models of complex physiological regulations for their further expansions – for example, the models of Guyton of 1972 [19], and Ikeda's models of 1979 [28]. This is the path taken, for example, by the SAPHIR (System Approach for Physiological Integration of Renal, cardiac and respiratory control) project international research team as the source texts of QHP model seemed very poorly legible and difficult to understand to the project participants [73].

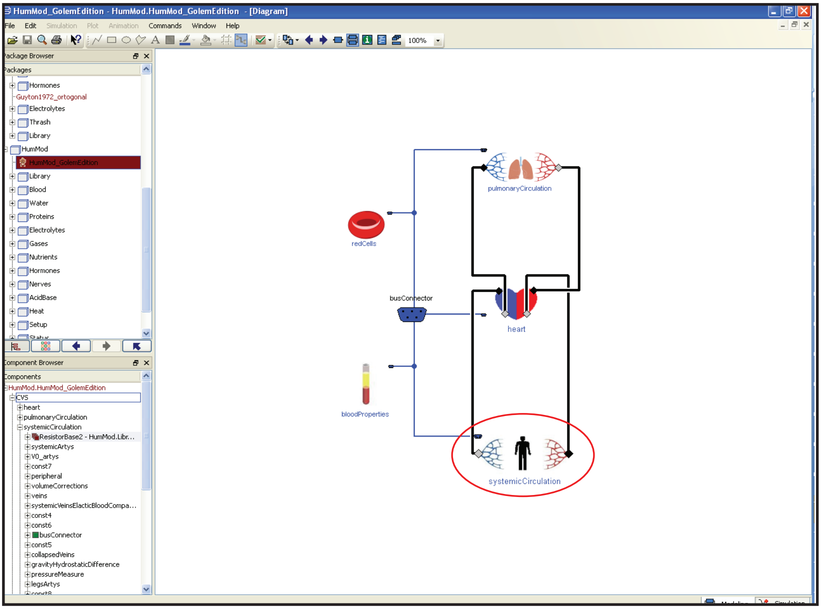

Figure 5: Inner structure of the cardiovascular component (class CVS from the previous figure).

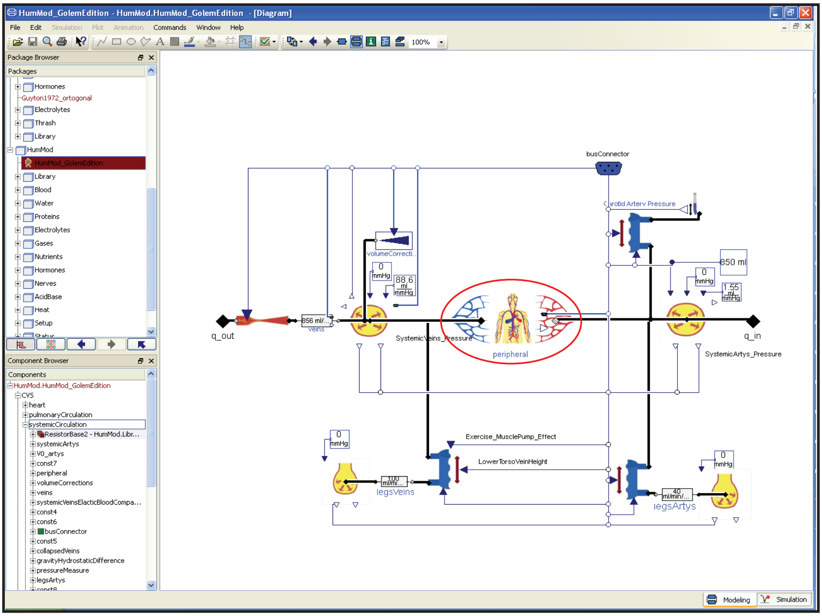

Figure 6: Inner structure of the system circulation component (class SystemicCirculation from the previous figure).

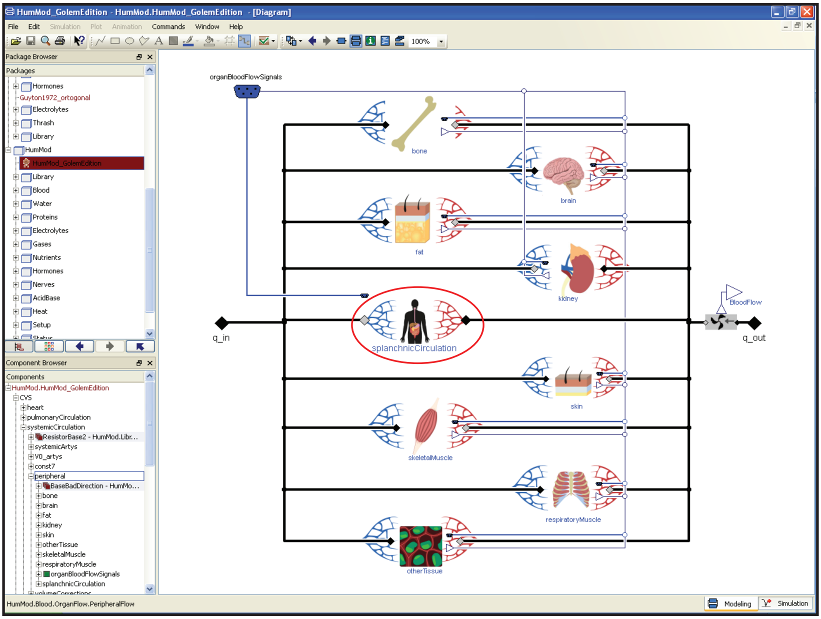

Figure 7: Inner structure of the system peripheral circulation component (class Peripheral from the previous figure).

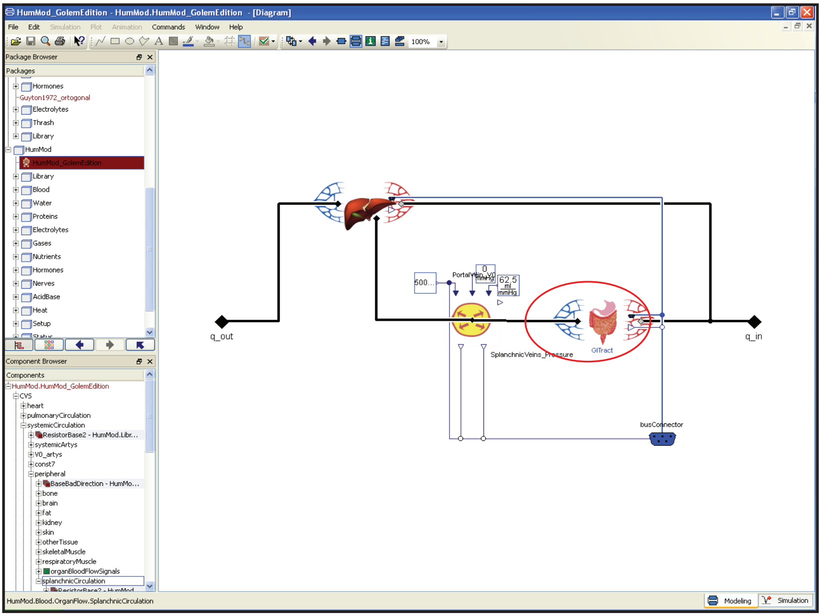

Figure 8: Inner structure of the splanchnic circulation component (class SplanchnicCirculation from the previous figure).

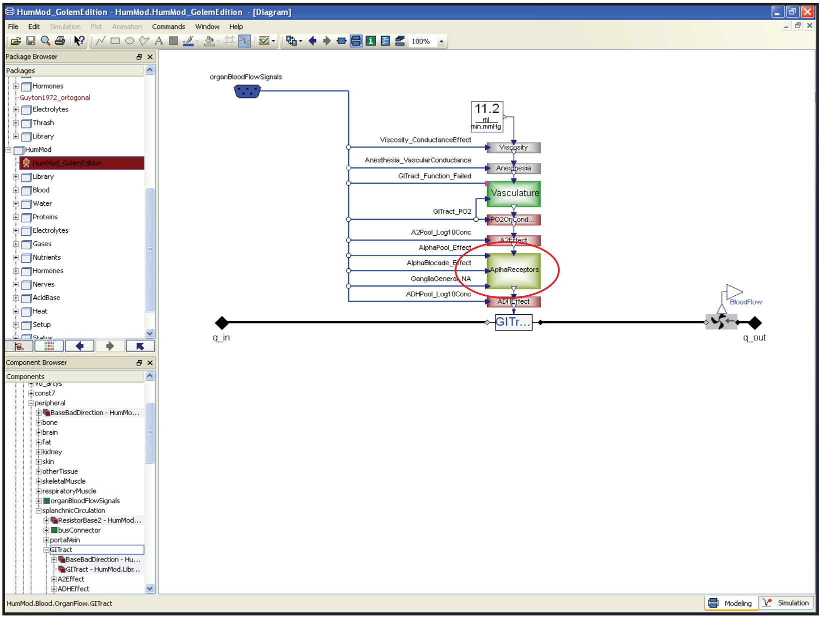

Figure 9: Inner structure of the gastrointestinal vascular resistance component (class GITtract from the previous figure).

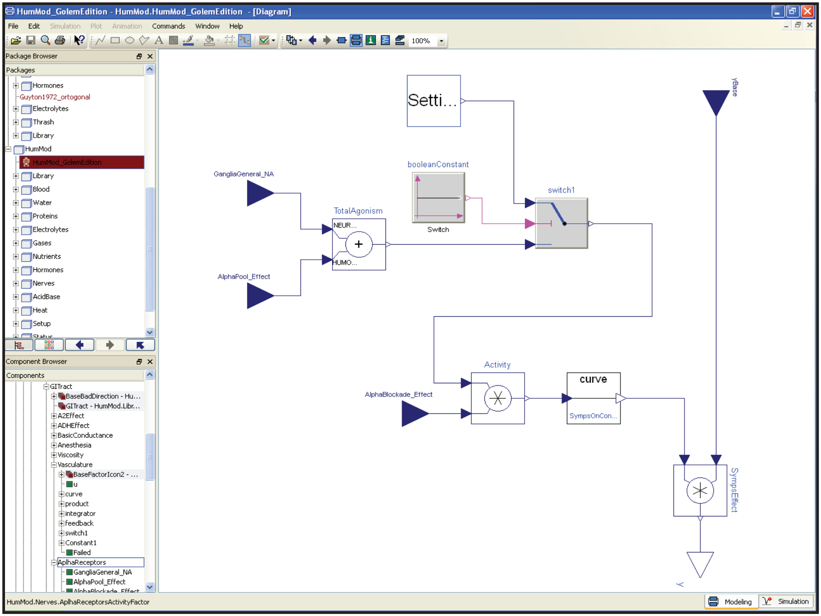

Figure 10: Inner structure of the component that calculates the effect of alpha receptor stimulation on gastrointestinal vascular resistance (class AlphaReceptors from the previous figure).

Similarly, Mangourova et al. [60] recently implemented an older Guyton's model of 1992 [7] in Simulink, rather than the most recent (poorly legible for them) version of the model QHP/Hummod of the team of Guyton's collaborators and students.

We were not discouraged and have established cooperation with the American authors. We have designed a special software tool ***QHPView*** [41] that creates a clear graphic representation of the mathematical relationships used, from thousands of files of source texts of the model. Besides others, this has also been helpful in discovering some errors in the model ***Hummod***.

Together with the American authors, we are of the opinion that source texts of the models that are the foundation of medical simulators should be publicly available given that they are the result of theoretic study of physiological regulations – then it is easy to find out to what extent the model corresponds to the physiological reality. The structure of our model called "***Hummod-Golem edition***" is published at the project website (http://physiome.cz/Hummod) in its source form, together with the definitions of all variables and all equations. Unlike the American colleagues, our model is implemented in Modelica, which makes it possible to provide a very clear expression of the model structure.

The model ***Hummod*** has been modified and expanded particularly in the field of blood gas transfer modelling and modelling of the homeostasis of the inner environment, especially of acid-base equilibrium – considering that disorders precisely of these subsystems occur frequently in acute medicine for which our simulator and educational simulation plays have been designed. Besides others, our modifications stemmed from our original complex model of physiological regulations, namely the core of the educational simulator ***Golem*** [37].

Illustrations of the hierarchic structure of the model Hummod-Golem Edition are shown in Figures 4-10.

The model allows form simulating a number of physiological and pathophysiological actions – failure of individual organs and organ systems, and subsequent adaptation responses of the body, the effect of any chosen therapy, response to physical load, and adaptation of the body to the change of some external conditions (for example, response to changed temperature). The integrated model of physiological systems ***Hummod-Golem edition*** is a theoretic foundation of the medical educational simulator ***eGolem***. However, its further development and identification are only the first kind of challenges to be faced. Another problem consists in programming the simulator itself as an educational aid. Our aim is to make the simulator available as a teaching aid available through the Internet. Our web simulator design technology described in greater detail in the habilitation thesis (http://www.physiome.cz/kofranek/habilitacni-prace.pdf) and in [14] will be used in its design.

9. From "art" to "industry"

The times of enthusiasts who created the first educational programs at the turn of the 80ies, excited about the new potential of personal computers, has long been gone. Today, the design of good-quality educational software capable of utilizing the potential offered by the development of information and communication technologies is not built on the diligence and enthusiasm of individuals. It is a demanding and complicated process of a creative team of specialists from various professions: Experienced teachers whose scenarios provide the foundation of a good-quality educational application; system analysts responsible, in cooperation with professionals of any given field, for the creation of simulation models for educational simulation plays; artists who design the external visual form of the simulator; and finally, information science specialists (programmers) who “stitch up“ the whole application to its final form [36].

For such interdisciplinary cooperation to be efficient, numerous developmental tools and methodologies are needed for every stage of development; such tools and methodologies make the work of individual team members easier and help them to overcome interdisciplinary barriers. Considerable efforts must be devoted to the process of creating and mastering the tools, but it pays in the end. The process of educational program design thus acquires ever more features of engineering design work.

10. References

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Study:

- 1967: School-leaving examination at the special Secondary School of Mathematics and Physics in Moscow
- 1967-68: First year study at the Faculty of Medicine, First Moscow Medical Institute
- 1968-1973: Continued study (years 2 – 6) at the Faculty of General Medicine, Charles University in Prague; graduated in 1973
- 1974-1980 Postgraduate study at the Institute of Pathological Physiology, Charles University
- 1982 – Successfully defended the postgraduate thesis (CSc.) at the Faculty of General Medicine, Charles University in Prague

Occupational positions:

- 1973-1974 Regular military service
- 1974-1980 Postgraduate study at the Institute of Pathological Physiology, 1st Faculty of Medicine, Charles University, and clinical work experience at the Department of Internal Medicine at Strahov
- Since 1980, lecturer at the Faculty of General Medicine, Charles University in Prague
- In 1990-1995, publisher of the specialized journal BAJT together with Ladislav Zajíček
- 1995 – present: Head of the Department of Biocybernetics and Computer-Based Teaching Support at the Institute of Pathological Physiology, 1st Faculty of Medicine, Charles University in Prague

Professional and scientific orientation:

Upon graduation, engaged in modelling and simulation for the study of physiological regulations. Simulation model of acid-base equilibrium of blood was the topic of his postgraduate thesis. The model of acid-base equilibrium of blood was expanded to create an extensive model of inner environment regulation. In the 80ies, cooperation in the design of extensive models of physiological regulations within the framework of the then Soviet cosmic research. At the same time, engaged in the use of simulation models for assessment of clinical-physiological data, and in using the models to explain the mechanisms of physiological regulations. During the last 15 years, engaged in the field of practical application of physiological system models in medical education, and related technologies of creating educational simulators, besides others. Built an interdisciplinary creative team at the Department of Biocybernetics and Computer-Based Teaching Support at the Institute of Pathological Physiology, 1st Faculty of Medicine, Charles University. Supervisor of postgraduate students (graduates of the Faculty of Medicine, Faculty of Mathematics and Physics of the Charles University, and Faculty of Electrical Engineering of the Czech Technical University) for the fields Biomedical Information Science, and Human Physiology and Pathophysiology. Gives lectures at the 1st Faculty of Medicine of the Charles University, and at the Faculty of Electrical Engineering of the Czech Technical University. At the same time, has been engaged in education of artists who cooperate in the design of the user interface of educational simulators. Therefore teaches the subject "Interactivity Control" at the College and High Art School of Václav Hollar.