

GUYTON'S DIAGRAM BROUGHT TO LIFE – FROM GRAPHIC CHART TO SIMULATION MODEL FOR TEACHING PHYSIOLOGY

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Abstract

Thirty five years ago, A.C. Guyton et al. published a description of a large model of physiological regulation in a form of a graphic schematic diagram. Authors brought this old large-scale diagram to life using Matlab/Simulink. The original lay-out, connections and description of individual blocks were saved. However, contrary to the old system analysis diagram, the new one is also a functional simulation model by itself, giving the user possibility to study behaviour of all variables in time. Furthermore, obvious and less obvious errors and omissions were corrected in the new simulink diagram.

1 Introduction

Prof. Arthur C. Guyton, T. G. Coleman and H. J. Grand published article [6] in the magazine Annual of Biomedical Physiology 35 years ago, which was completely different form usual physiological articles published until that time. It's fundament was large scheme, which at first sight evoked some electrotechnical device, but there were shown computing blocks (multipliers, dividers, simulators, integrators, functional blocks) instead of valves or electrotechnical components. They symbolized mathematical operations, which were applied on physiological quantities. Connecting wires between blocks represented complicated feedback connections of physiological quantifies. Blocks were divided to eighteen groups, which have represented separate physiological subsystems. Central subsystem symbolized circulation dynamics – to which were connected other blocks (kidney, tissue fluid, electrolytes, hormonal control and autonomous nervous regulation) via feedback connections.



Figure 1: Dr. Arthur C. Guyton, with medical students discussing his computer model of cardiovascular system

2 Schematic diagram instead of verbal description

The article described a large-scale model of the circulatory system regulation in wider perspective: The respiratory system is integrated into other subsystems of the organism that influence its function. Instead of giving the reader set of mathematic equations, the article uses fully equivalent graphical representation. This syntax graphically illustrates the mathematical relationships in the form of the above mentioned blocks. The description of the model was given in the form of the principal graphical chart only (which was, however, fully illustrative), explicatory comments and reasoning behind the given formulas were very brief, e.g.: “Blocks 266 through 270 calculate the effect of cell pO₂, autonomic stimulation, and basic rate of oxygen consumption by the tissues on the actual rate of oxygen consumption by the tissues.” Such a formulation required full concentration, as well as some physiological and mathematical knowledge for the reader to understand the meaning of the formalized relationships between the physiological entities. Later, in 1973, and in 1975 Arthur C. Guyton published monographs [7,8], where he explained most of the concepts in more length

Guyton's model represents the first large-scale mathematical description of the body's interconnected subsystems and their functioning. It was indeed a turning-point – the impetus to start

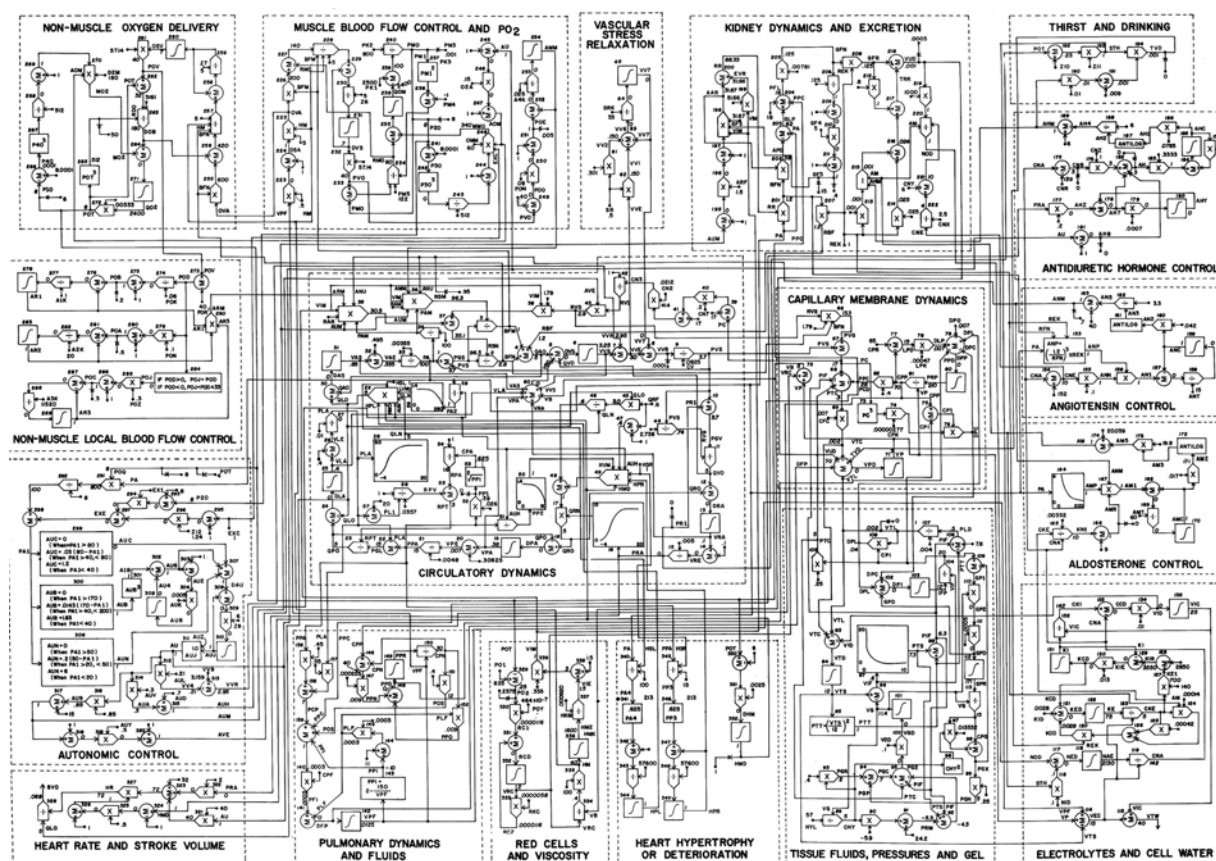


Figure 2: Overall regulation model of Circulation - original scheme by A.C. Guyton et al., 1972. Reprinted, with permission, from the *Annual Review of Physiology*, Volume 34 (c)1972 by Annual Reviews www.annualreviews.org

When you study the dynamism of regulatory processes, verbal description and common sense are often not sufficient. Prof. Guyton has realized that already in the mid sixties when he studied the factors influencing blood pressure. Hence, he has searched a more exact way of expressing relationships, first using connected graphs and finally also computer models. He created his first computer models, together with his long term colleague Thomas Coleman, in 1966. As an erudite physiologist and a hand-minded person at a same time, he was engaged in biomedical engineering in times, when this specialization did not yet officially exist.

Remarkably, Guyton did not intend to engage in theoretical medicine at first. His original aim was to work in the clinical field. After the graduation from the Harvard University in 1943, he began his surgical internship at Massachusetts General Hospital. His surgical carrier was interrupted by war. He was called into Navy. However, he worked in bacteriological warfare research during most of this period. After the war, he returned to the surgery, but only for a short while. In 1946, overworked, he suffered a bout of poliomyelitis that left serious consequences – paralysis of the left arm and leg has bound him either to wheelchair or crutches for the rest of his life. However, his creative spirit did not leave him in the period of hardship and he has invented an electric wheelchair controlled by “a joystick”, as well as a special hoist for easy transfer of disabled people from bed to the wheelchair. Later, he has received a Presidential Citation for his invention. The physical handicap ended Guyton’s carrier in cardiac surgery and steered him into the theoretical research. In spite of having job offers at the Harvard University, he returned back to his hometown Oxford, Mississippi, where he first taught pharmacology at two year medical school; however, not a long time after that, he became a head of Department of Physiology at University of Mississippi. He has established a world famous physiological school in what used to be a rather provincial institute (on American scale). Here, he wrote his world-famous textbook of physiology, originally a monograph that has seen its eleventh edition already, as well as more than 600 articles and 40 other books. He has trained many generations of medical students and more than 150 Ph.D. students. In 1989, he has passed on the leadership of the

institute to his disciple J.E. Hall and as a professor emeritus devoted himself to research and teaching. He has died tragically in an automobile accident in 2003.

4 Fixing errors in Guyton's chart

Guyton was among the first proponents of the formalized description of physiological reality. Formalization means converting a purely verbal description of a relevant array of relationships into a description in the formalized language of mathematics. Guyton's diagram from 1972 (Fig 2) is a formalized description of results of one of the first significant systemic analysis of physiological functions.

Graphic notation for description of quantitative and structural relations in physiological systems suggested by Guyton was adopted by other authors in the seventies and eighties. For example, in 1977 [2] used slightly modified Guyton's notation in their monograph, covering the system analysis of interconnection between physiological regulation systems, [11] formulated, in Guyton's notation, their model of overall regulation of body fluids etc.

Later on, for graphic notation of structure of physiological regulation relations, were used means of simulation development tools, for example, Simulink by Mathworks company or open source free software package for teaching physiological modelling and research JSIM [16, 17] (see <http://www.physiome.org/jsim/>), or recently, graphic means of expression of simulation language Modelica [5].

Simulink diagrams are very similar to the thirty-five year old notation used in the original model of A.C.Guyton. Therefore we decided to revive the old model by means of a modern software instrument. We tried to keep the resemblance identical as it was in the original pictorial diagram - the layout, the disposition of wires and the quantity labels are the same.

The realization of the old diagram is not as smooth as it might seem at first sight because there are errors and omissions in the original scheme. In a hand-drawn picture, they do not matter so much, because the overall meaning is still valid (most of the errors are present just on the paper, not in the original FORTRAN implementation). However if we try to bring the model to life in Simulink, the errors show. The model either behaves inadequately or even becomes unstable, values of start to oscillate and model complex collapses. There were a few errors – changed signs, multiplier instead of divider, changed connection between blocks, missing decimal point, wrong initial conditions etc. – but it was enough for wrong function of the model. Being acquainted with physiology and system analysis, we could have avoided the mistakes with a little effort.

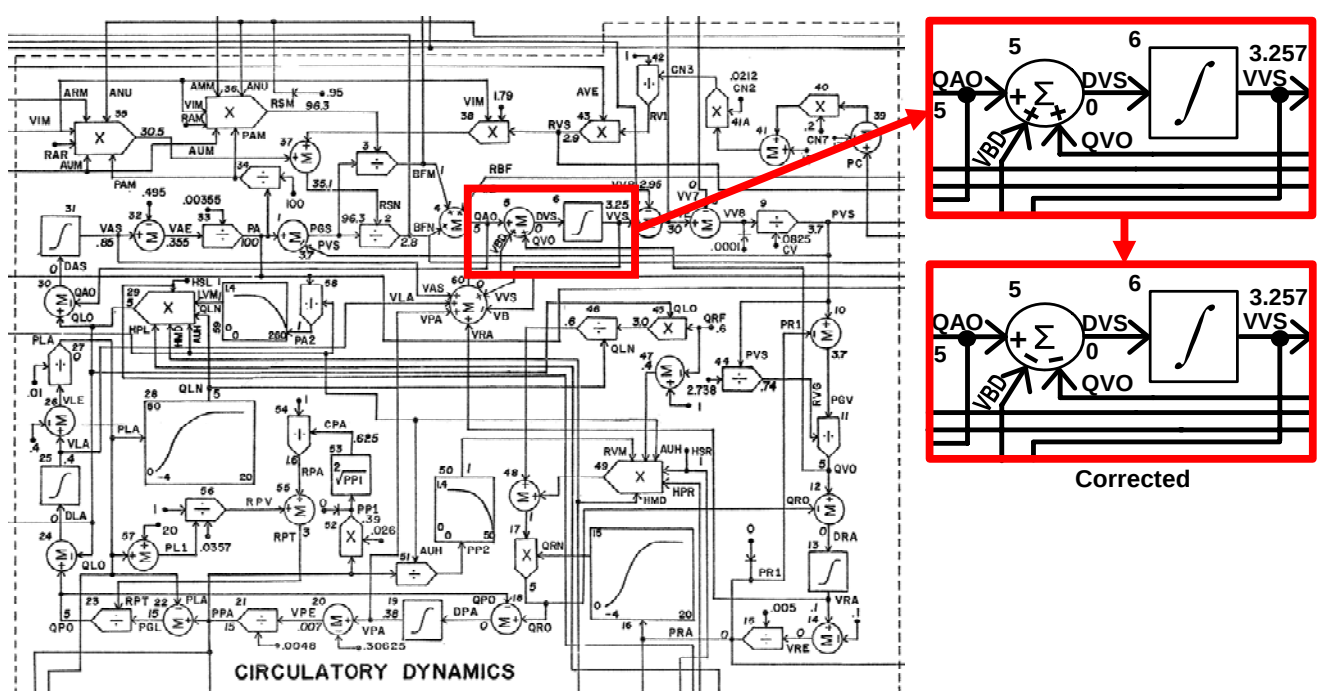


Figure 3: The error in the subsystem Circulatory Dynamics

Easily detectable error in the diagram is, for instance, wrong marking of flow direction in the summation block no. 5 in subsystem Circulatory Dynamics (Fig 3). It is obvious, that the rate of increase in systemic venous vascular blood volume (DVS) is the subtraction (not the summation) between all rates of inflows and rates of outflows. Inflow is a blood flow from systemic arterial system – its rate is denoted as QAO, outflow rate from systemic veins is a blood flow rate from veins into right atrium (QVO). Rate change of filling of vascular system as the blood volume changes (VBD) is calculated from the difference between summation of overall capacity of vascular blood compartments and blood volume – therefore VBD is the outflow rate and not the inflow rate, and in the summator it must have a negative sign.

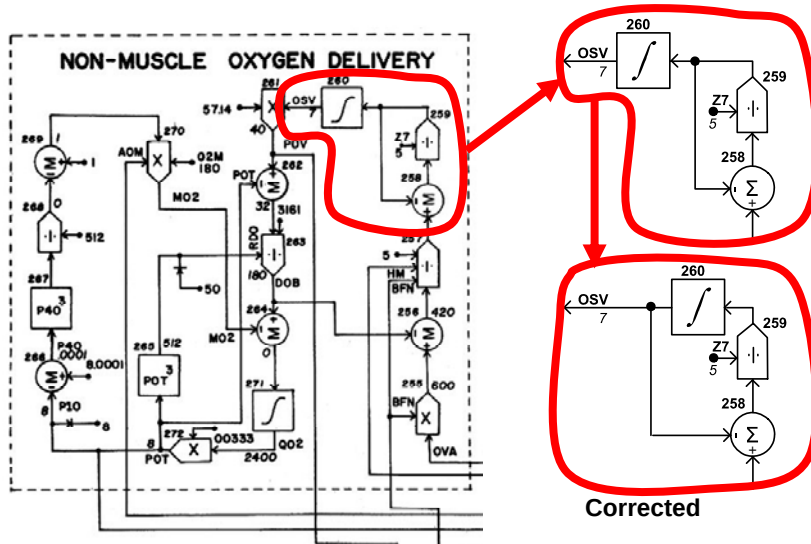


Figure 4: The error in the subsystem Non-Muscle Oxygen Delivery

In subsystem Non-Muscle Oxygen Delivery, there is a wrong depiction of connection in integrative block no. 260 (Fig.4). If the model was programmed exactly as depicted in the original diagram, the value of non-muscle venous oxygen saturation (OSV) would constantly rise and the model would become unstable very quickly. Besides, there would be an algebraic loop in the model. Correction is simple, input to summator no. 258 is value OSV, therefore it is sufficient to move feedback input to summator behind the integrator as it is indicated in the picture.

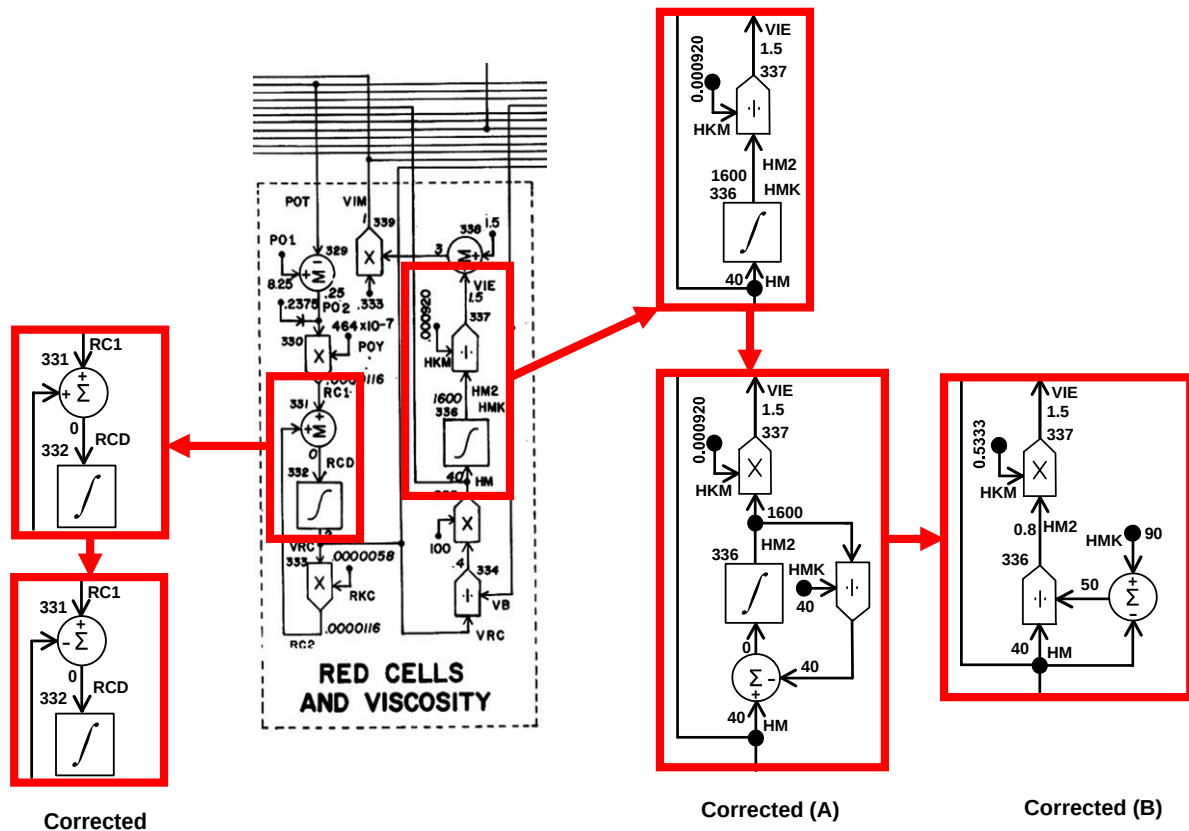


Figure 5: The errors in the subsystem Red Cells and Viscosity

Small and simple subsystem Red Cells and Viscosity includes two errors (Fig 5). The first is visible at first sight. It is obvious that the rate of change of red cell mass (RCD) is the subtraction (not the summation) between red cell mass production rate (RC1) and red cell mass destruction rate (RC2). The second error is obvious as well. During calculation of portion of blood viscosity caused by red blood cells (VIE) from value of hematocrit (HK) according to the diagram, the viscosity would have to constantly rise, because the value of quantity HM2 would incessantly rise (HK is the input to the integrator). According to the diagram, the value of a variable HM2 is equal to 1600 - in stable situation and under normal conditions. If we divide this value by a constant parameter HKM ($=0.000920$), we should arrive at normal value VIE. Normal value VIE should be 1.5 (formulated as a ratio to viscosity of water). We can find out, by simple calculation, that it is not so, and we will arrive at correct calculation if we multiply value HM2 by constant HKM instead of division. Thus it is obvious, that block no. 337 should be multiplier unit and not dividing unit. In order to have value of a variable HM2 in stable situation constant (and under normal conditions equal to value 1600), the input to integrator must have (block no. 336) zero value. Therefore, it is apparent, that the depiction of feedback has been omitted in the diagram. Corrected diagram is shown in picture 6 as "Corrected (A)". Viscosity is proportionate to hematocrit and the integrator acts here as dampening element. From experimental data can be derived, that dependence of viscosity of blood on hematocrit is not linear proportionate [7]. Therefore in later realization of the model (according to source text in Fortran language) was the relation between hematocrit (HK) and portion of blood viscosity caused by red blood cells (VIE) formulated as follows:

$$VIE = \frac{HM}{(HM - HMK)HKM} \quad (1)$$

Where:

$$HMK = 90$$

and

$$HKM = 5.3333$$

which is shown in a diagram in fig. 6, marked as Corrected (B). If we compare this picture with the original chart; the integrator no. 336 is replaced with dividing and summator units (and the value of HKM constant is quite different). Maybe, this exact structure should have been originally drawn in the original diagram, and (by mistake, the integrator was drawn instead of divider and summator). A label HKM on the left side next to integrator no. 336 indicates this situation.

An error in subsystem Antidiuretic Hormone Control is not visible at first sight (Fig. 6). According to graphic diagram, the following should hold true:

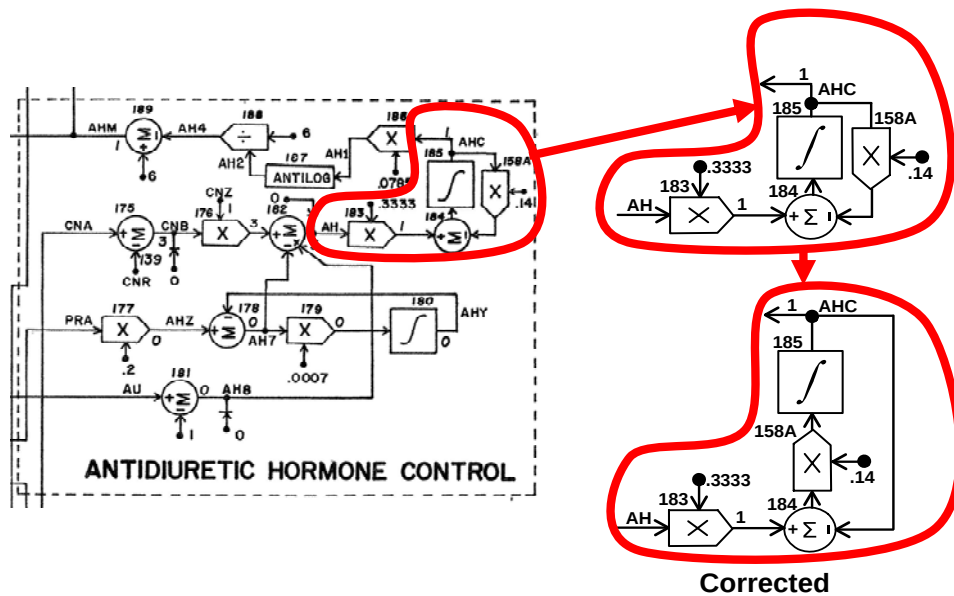


Figure 6: The error in the subsystem Antidiuretic Hormone Control

During stable condition, according to data on graphic diagram under normal conditions, the values should be:

$$\begin{aligned} 0.333 AH &= 1, \\ AHC &= 1. \end{aligned}$$

Then the integrator 185 will have no zero value and the system will not be in stable condition.

Where is the error?

$AH*0.3333$ is a normalized rate of antidiuretic hormone creation (ratio of current rate of creation according to the norm). AHC is normalized concentration of this hormone (according to the norm). How is calculated the normalized concentration of substance from normalized rate of substance creation? Classic compartment approach will answer our question.

In subsystems of conducting ADH creation, aldosterone and angiotensin are calculated in a model from the rate of hormone inflow (normalized as a relative number according to the norm) hormone concentration (again normalized as a relative number according to the norm).

We come out of a simple compartment approach - into whole-body compartment inflows hormone at the rate F_i (it is synthesised) and outflows at the rate F_o . Quantity of hormone M in whole-body compartment depends on balance between inflow and outflow of the hormone.

$$F_i - F_o = \frac{dM}{dt}. \quad (2)$$

Rate of depletion of hormone F_o is proportional to its concentration c :

$$F_o = k c. \quad (3)$$

Concentration of hormone c depends on overall quantity of hormone M and on capacity of distribution area V :

$$c = \frac{M}{V}. \quad (4)$$

Thus after inserting:

$$F_i - \frac{k M}{V} = \frac{dM}{dt}. \quad (5)$$

Provided that the capacity of distribution area V is constant, we will substitute ratio k/V for constant k_1 :

$$k_1 = \frac{k}{V}. \quad (6)$$

We arrive at:

$$F_i - k_1 M = \frac{dM}{dt}. \quad (7)$$

In the model, Guyton calculated the concentration of hormone c_0 normalized as a ratio of current concentration c to its normal value c_{norm} :

$$c_0 = \frac{c}{c_{norm}}. \quad (8)$$

At invariable distribution area V ratio of concentrations is the same as a ratio of current overall quantity of hormone M to overall quantity of hormone under normal conditions M_{norm} :

$$c_0 = \frac{c}{c_{norm}} = \frac{M}{M_{norm}}. \quad (9)$$

If we formulate the rate of flows in a normalized way (as a ratio to normal rate), then under normal conditions:

$$\begin{aligned} F_i &= 1, \\ \frac{dM_{norm}}{dt} &= 0. \end{aligned}$$

Therefore:

$$1 - k_1 M_{norm} = 0 . \quad (10)$$

Normal quantity of hormone M_{norm} will be:

$$M_{norm} = \frac{1}{k_1} . \quad (11)$$

Hence, the relative concentration of hormone c_0 can be formulated:

$$c_0 = \frac{M}{M_{norm}} = k_1 M . \quad (12)$$

Thus:

$$M = \frac{c_0}{k_1} . \quad (13)$$

After inserting into differential equation we arrive at:

$$F_i - k_1 \frac{c_0}{k_1} = \frac{d\left(\frac{c_0}{k_1}\right)}{dt} , \quad (14)$$

i.e.:

$$F_i - c_0 = \left(\frac{1}{k_1}\right) \frac{dc_0}{dt} . \quad (15)$$

Thus:

$$(F_i - c_0)k_1 = \frac{dc_0}{dt} . \quad (16)$$

According to this equation, the normalized concentration of hormone c_0 is calculated from the normalized inflow of hormone F_i . In original Guyton's chart, the normalized concentration of aldosterone and angiotensin is calculated in this way. In case of ADH, there is an error in the chart .

The normalized rate of inflow in case of ADH:

$$F_i = 0.3333 AH . \quad (17)$$

The normalized concentration of hormone is:

$$c_0 = AHC , \quad (18)$$

Coefficient $k_1 = 0.14$.

Instead of $(F_i - c_0)k_1 = \frac{dc_0}{dt}$, there is a graphic representation of relation $F_i - c_0 k_1 = \frac{dc_0}{dt}$.

Correct relation in case of ADH should be:

$$(0.3333 AH - AHC)0.14 = \frac{dAHC}{dt} . \quad (19)$$

This relation corresponds to correct part of diagram shown in fig. 6

Quoted examples of errors in original graphic depiction of Guyton's model do not mean at all, that the actual implementation of the model did include the above-mentioned errors. The model was implemented in Fortran language and it functioned flawlessly. Incorrect was only the graphic depiction of mathematical relations that did not correspond to the model. If somebody implemented the model exactly according to the depiction, without thinking over and understanding the meaning of mathematical relations between physiological quantities, then such a model would not function correctly on a computer.

It is interesting, that this complicated schematic diagram was many times overprinted in several publications and nobody made an effort to fix these errors. After all, at the time, when picture schemes were created no appropriate application had existed yet – picture arose like a complicated drawing – and to handle redoing such a complicated drawing isn't so easy. Maybe the authors didn't even want to

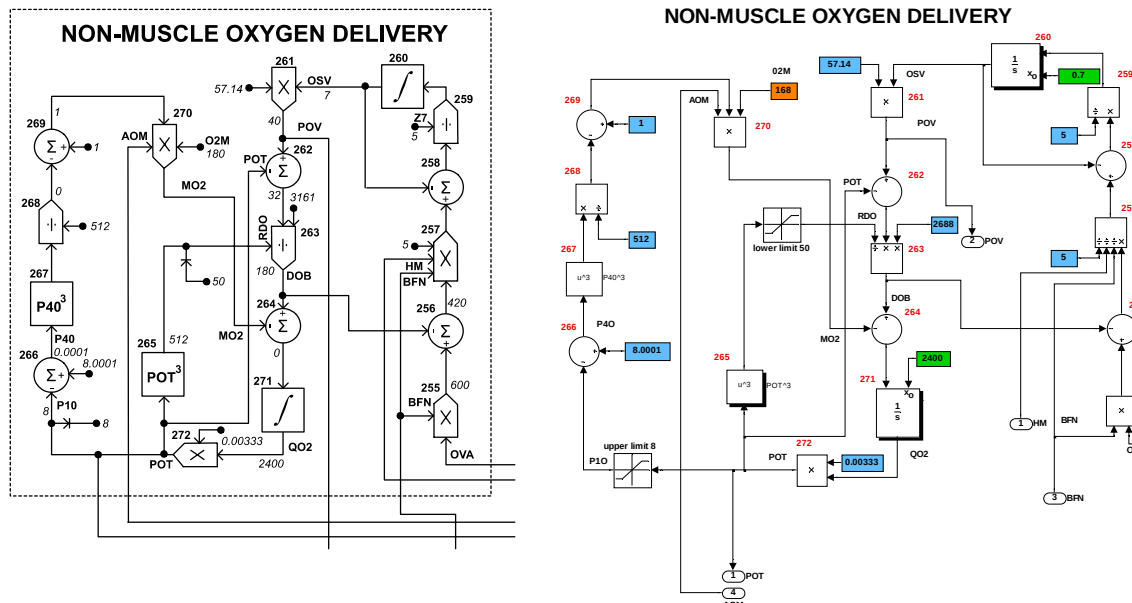


Figure 7: The pictorial block scheme of the original A.C. Guyton's model on the left and the model block diagram in the Simulink software tool. Analogically positioned and numbered blocks represent the same mathematical operations. Multipliers and dividers: blocks 255, 257, 259, 261, 263, 268, 272, 270; sum blocks: 256, 258, 262, 264, 266, 269; integrator blocks: 260 and 271; function blocks (cubic function): 265 and 267; high level saturation: between blocks 272 and 286, low level saturation: between blocks 265 and 180. The switches can either be set to receive the input values from other subsystems, or directly from the user, thus disconnecting the block from the rest of the model.

correct the errors - who took the pain over analysis of the model, easily uncovered the diagrams mistakes - who wanted just blindly copy, failed. After all, at that time, the authors even used to send round the program source files in Fortran language, so if somebody wanted just test the behaviour of the model he hadn't to program anything (at most routinely converted the Fortran program into other programming languages).

5 Results

After correction of errors in the original Guyton's chart, we realized its Simulink implementation. In Simulink diagram, we tried to maintain the same distribution of all individual elements, as in original diagram.

The only difference is in the graphic shapes of individual elements - e.g. in Simulink, the multiplier/divider is represented as a square unlike the "piggy" symbol in the Guyton's notation (See Fig. 7). The integrator has not the sign of integral on itself but the expression "1/s" (being related to the transcription of Laplace transformation).

In the Simulink model, we used also switches by which we could couple or uncouple individual subsystems and control loops.

Resultant chart of Simulink model is depicted in Fig 8.

We can transform individual physiological subsystems of the model into form of Simulink subsystems. Graphic chart of the whole model looks rather better arranged (Fig. 9). Then the diagram of the model resembles the interconnected network of electronic chips – instead of electric signals, however, there is a flow of information in individual conductors - data of the model. Physiological subsystems are represented by "simulation chips" – to their individual input "pins" are connected conductors with input data and from their output "pins" to other "simulation chips" are distributed signals with information about the value of individual physiological quantities. Models formulated through network of "simulation chips" are also the appropriate tool for team collaboration between branches of study [13]. Such a chart is much more legible also for an experimental physiologist, who

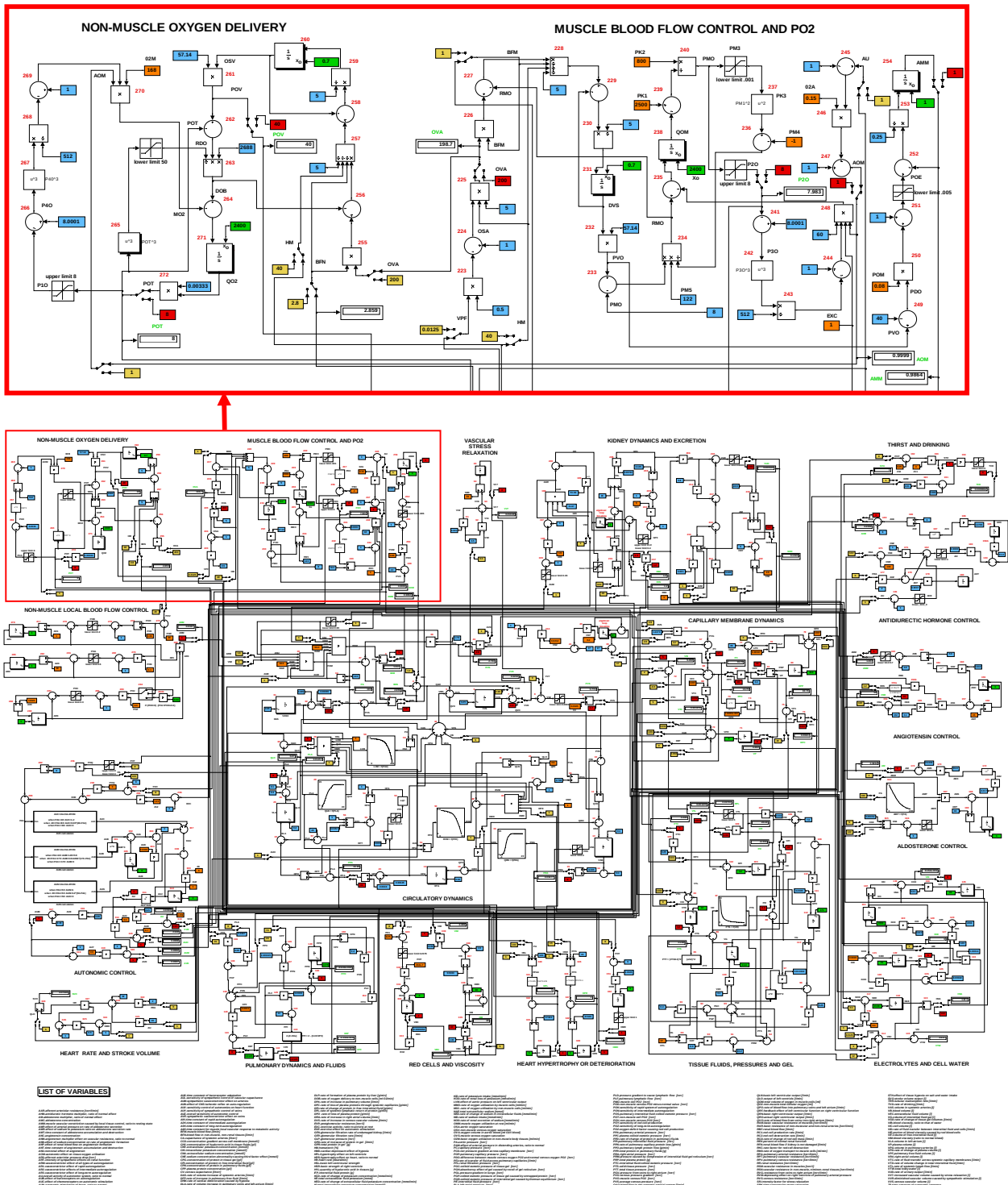


Figure 8: Guyton's overall regulation model of Circulation - implementation in Matlab/Simulink. The layout and block numbering is exactly the same as in the original Guyton's scheme (Fig. 2). The difference is, that this scheme is also a fully functional simulation model.

does not have to understand the complicated mathematical structure of computational network inside a "simulation chip", however he understands the structure and functions of physiological relations. He can study the behaviour of a model in individual simulation chips on virtual displays and oscilloscopes, that are standard components of Simulink environment.

In fig. 10, there is a Simulink implementation of a Guyton-Coleman model from 1986, formulated with the help of interconnected "simulation chips". When the reader compares it to a previous picture, he can imagine how the model has expanded in past 14 years.

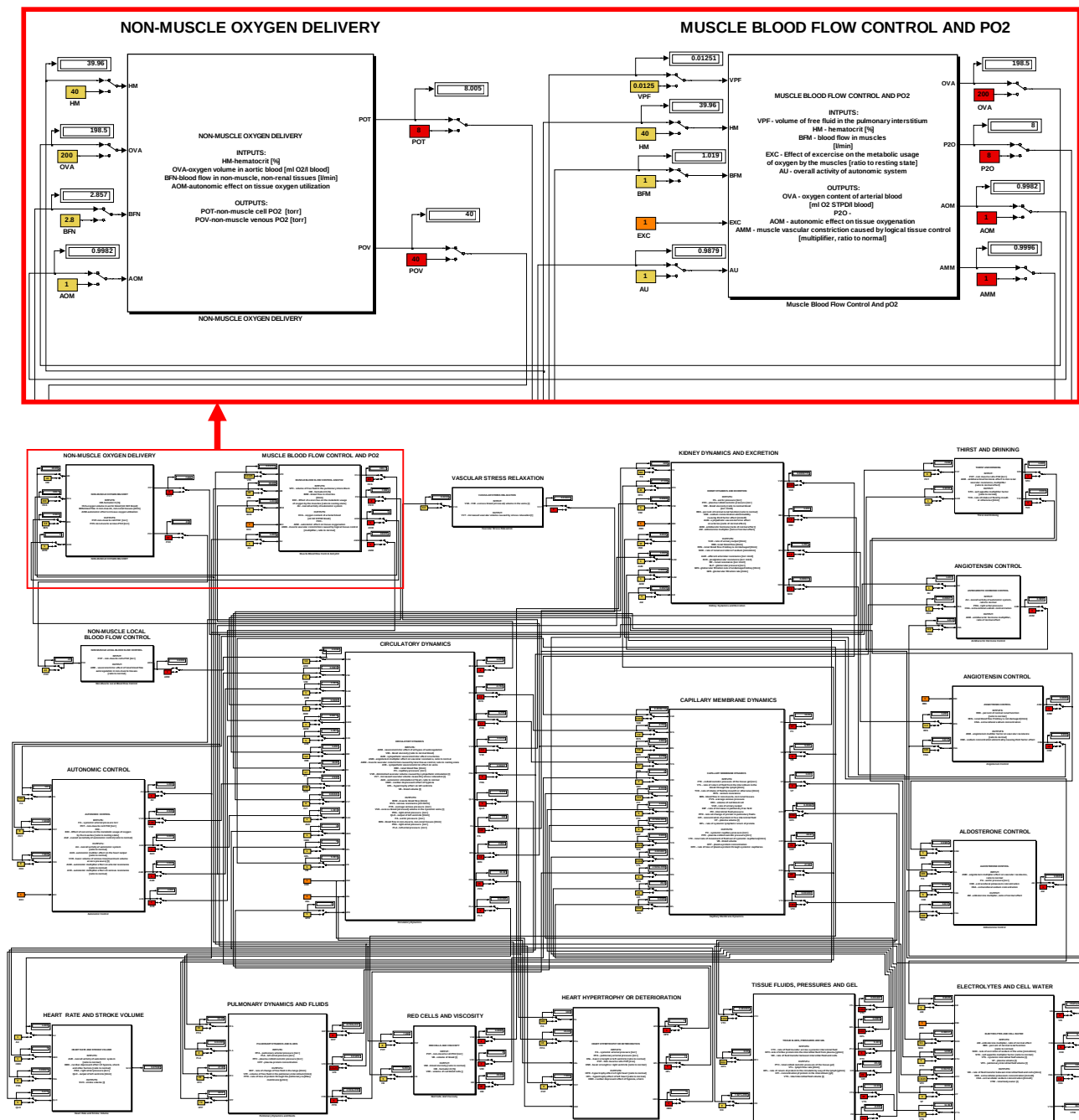


Figure 9: Guyton's overall regulation model of Circulation - implementation in Matlab/Simulink using Simulink subsystem blocks as "simulation chips".

Simulink implementation of the (corrected) Guyton's model made by us is available for download at the address <http://physiome.cz/Guyton> to everyone interested. At the same address, our Simulink implementation of a much complex sequel of the model from 1986 can be found, too. Further, there is also a detailed description of all mathematical relations used with their reasoning (however, for the present in Czech language only).

6 From Simulink diagram to simulation games during physiological teaching

We use Simulink implementation of Guyton's model as an educational tool to teach physiology to undergraduate and postgraduate students at ČVUT. This structure of Simulink diagram (in a form of "simulation chips") is, however, too abstract for medical students. It is ideal, if their teaching models have the form of schematic pictures to which they are accustomed, for example from atlas of physiology [18]. Unlike the book, these pictures can be interactive and models running on the

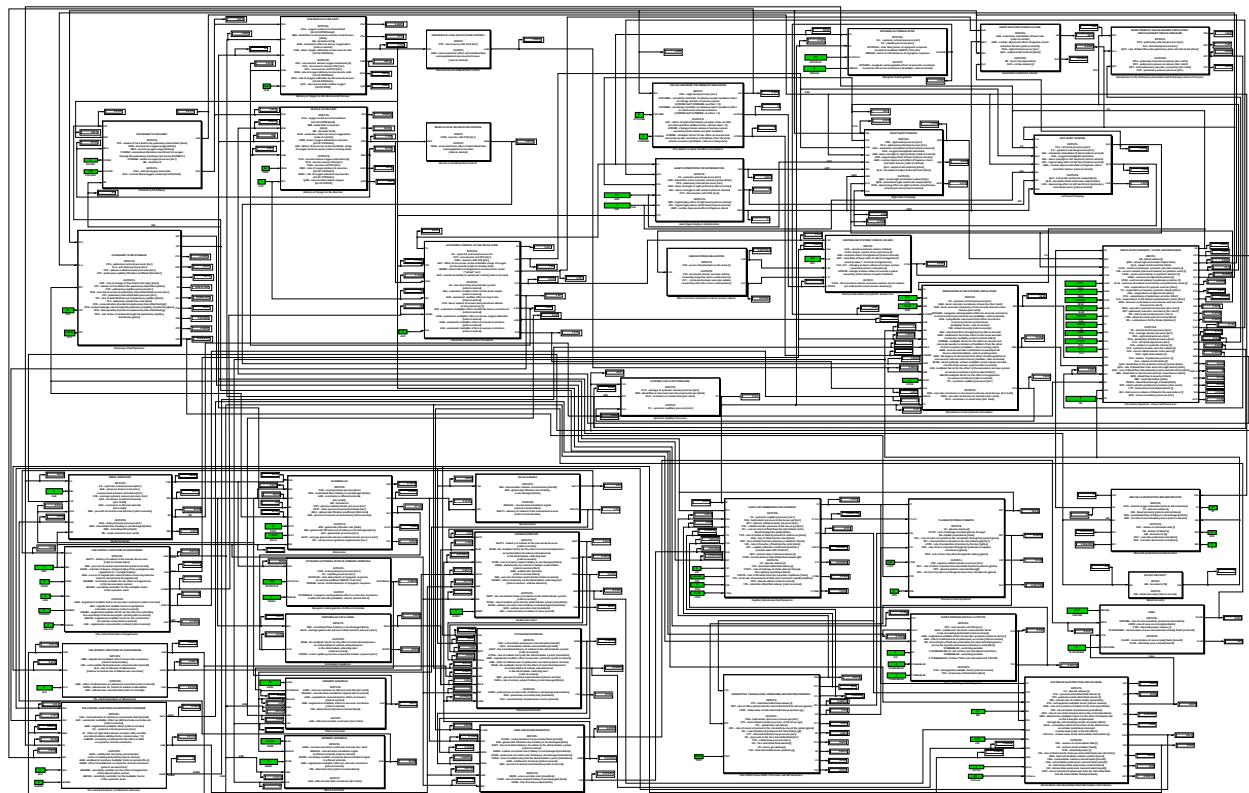


Fig 10. Simulink implementation of a Guyton-Coleman model from 1986.

background can enable students to "play" with this physiological subsystem and monitor its response to various inputs.

Simulation models on the background of teaching programs are therefore very effective educational tools that facilitate comprehension of complex regulation relations in human organism and pathogenesis of their malfunction.

From pedagogical perspective it is advantageous, according to our experiences, if we allow disconnection of individual regulation loops temporarily and study reaction of individual subsystems separately, which contributes to better understanding of dynamics of physiological regulations [12].

During creation of teaching applications with use of simulation games, it is necessary, on the one hand, to resolve the creation of simulation model, and on the other hand the creation of own simulator. These are two different tasks, whose effective solution facilitates the use of various developmental tools [14].

During creation of simulation models it is advantageous to use developmental tools designated for creating and identification of simulation models – for example Matlab/Simulink from Mathworks company. In this environment, we have also created a special library of physiological models - *Physiology Blockset for Matlab/Simulink, open source software library*. 1st Faculty of Medicine, Charles University, Prague, available at <http://physiome.cz/simchips>.

Creating simulation models is closely related to issues of creating formalized description of biological reality, which is the content of worldwide project PHYSIOME [3, 10].

Creating own teaching simulators is done in the environment of classic developmental tools for computer programmers (for example Microsoft Visual Studio etc.) and tools facilitating the creation of interactive animated pictures, used in user interface of teaching programs (for example Adobe Flash, Adobe Flex). Future probably lies in simulators available on web and on accessibility of e-learning educational environment [15, 19].

7 From simulation games to medical simulators

Thirty-five years ago, when A. C. Guyton et al. published his large-scale model, the only possibility to study the behaviour of the model was on large computers that often occupied an entire room. Nowadays it is possible to run even very sophisticated models on PC. Moreover, today's technology allow to add on graphical attractive user-friendly interface to these models.

From technological standpoint there are no obstacles that would prevent PCs from running learning simulators for practicing medical decision-making. The basis for pilot's simulator during training pilots is the model of the plane. Similarly, one of the prerequisites when creating medical simulator is the extensive simulation model of human organism. This simulation model must include all significant physiological subsystems – circulation, respiration, kidney function, water, osmotic and electrolyte homeostasis, acid-base regulation etc. – that have to be interconnected in the model. Therefore now is the time of renaissance in the formation of large integral models of human organism and concept of integrative physiology, that Gyuton came up with years ago - at the present time the practical fulfillment is being achieved.

For example at the present time, Thomas Coleman, one of the co-authors of a legendary article by prof. Guyton from 1972 [6], together with Guyton's disciples created a simulator Quatitative Human Physiology (QHP), whose theoretical basis is a new mathematical model of integrative human physiology which contains more than 4000 variables of biological interactions. Preview edition of this simulator is freely downloadable from the site <http://physiology.umc.edu/themodelingworkshop/>.

Simulator consists of two software packages.

The first is the equation solver, named QHP 2007.EXE. This is the executable file, prepared for the Windows operating system (2000, xp, Vista).

The second is an XML document that defines the model, the solution control and the display of results. This document is distributed over a large number of small files in the main folder and several subfolders. The XML schema used is described in preliminary fashion in another section of this modeling workshop.

The XML document is parsed at program startup. Parsing progress is displayed in the status bar at the bottom of the program's main window.

All of the XML files are both machine and human readable. You only need a text editor (such as Notepad, WordPad).

Unfortunately, the orientation in the structure of such a large model is difficult, due to a large number of variables (more than 4000).

Standardized notation of model structure in XML is easily understandable for the machine, but for a human it is necessary to provide graphic depiction of structure of physiological regulation relations.

Thus the suggestions that prof. Guyton et al. sparked, thirty-five years ago, by his legendary article (concept of integrative physiology, creation of large-scale models of integratively interconnected physiological subsystems and an effort to graphically depict the structure of physiological regulation relations), return nowadays in a new form and with new possibilities.

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