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. The authors brought this old large-scale diagram to life using Matlab/Simulink. The original layout, 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 a possibility to study behaviour of all the 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 the article [6] in the Annual Review of Physiology magazine 35 years ago. It was a completely different form of article than usual physiological articles published until that time. Its fundament was a large scheme, which at first sight evoked some electrotechnical device, but there were computing blocks shown (multipliers, dividers, summators, integrators, functional blocks) instead of electrotechnical components. They symbolized mathematical operations, which were applied on physiological quantities. Connecting wires between blocks represented complicated feedback connections of physiological quantifiers? Blocks were divided to eighteen groups, which have represented separate physiological subsystems. The central subsystem symbolized circulation dynamics – to which other blocks were connected (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 a 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 a 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

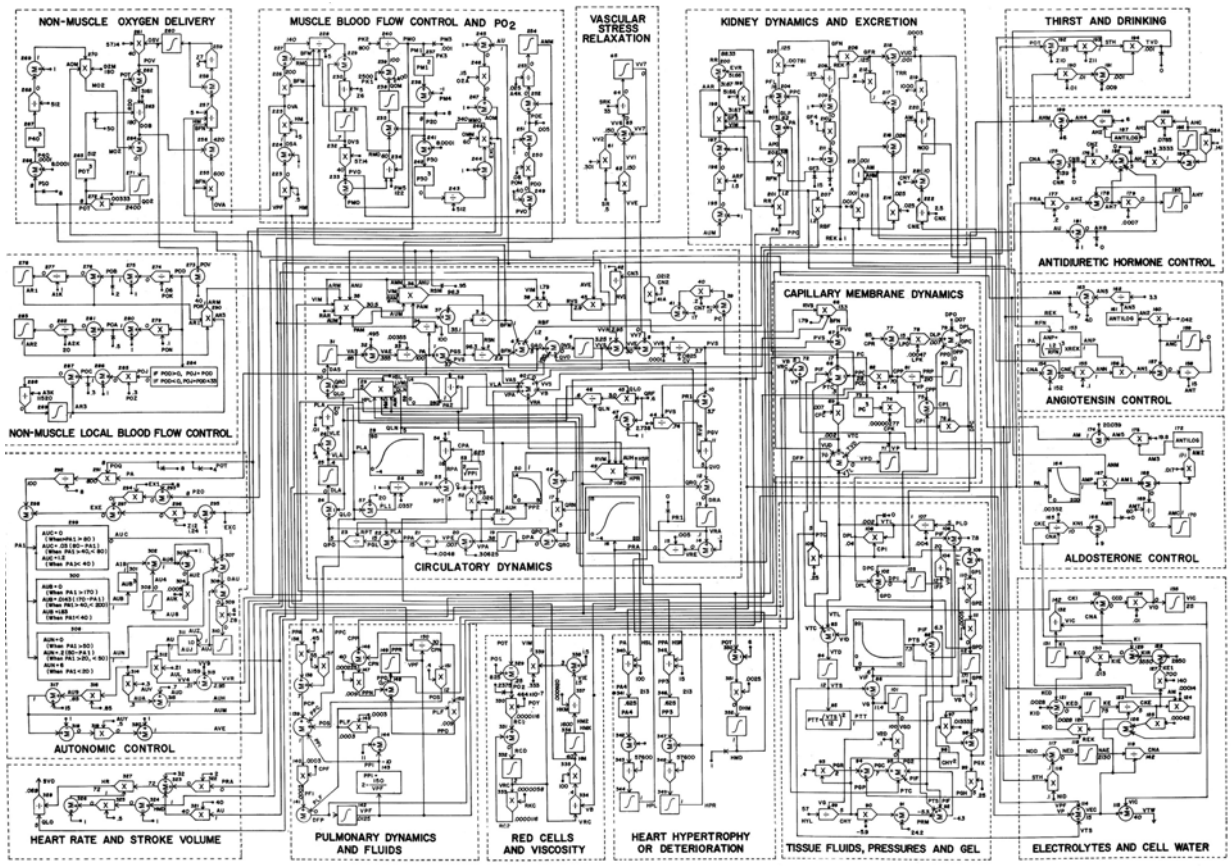

Figure 2: Overall regulation model of Circulation - original scheme by A.C.Guyton et al., 1972. Reprinted, with permission, from the Annual Review of Physiology, Volume 34 (c)1972 by Annual Reviews www.annualreviews.org

the research in the field known as integrative physiology. Using the system analysis of the physiological regulation, the model was for the first time in history able to depict the simultaneous dynamics of the circulatory, excretory, respiratory and homeostatic regulation.

The group of A. C. Guyton kept upgrading and extending the model later on, and upon request they even provided the FORTRAN source code of the model realization to the ones interested. In 1982, the "Human" model appeared [4], representing yet another milestone in the simulation model development. It gave the possibility to simulate a number of pathological conditions on a virtual patient (cardiac, respiratory, kidney failure, etc.) and the therapeutic influence of various drugs, infusions of electrolytes, blood transfusion, etc. Furthermore, the effect of the artificial organ use on normal physiological functions could have been simulated (artificial heart, artificial ventilator, dialysis, etc.). Its current interactive web implementation is available from this addresshttp://venus.skidmore.edu/human.

The latest work results from Guyton's colleagues and students are Quantitative Circulatory Physiology and Quantitative Human Physiology simulators [1]. Models can be downloaded from this address http://physiology.umc.edu/themodelingworkshop/**.**

3 Pioneer of the Systemic Approach in Physiology

Arthur C. Guyton (Fig. 1) was among the pioneers of system analysis in the inquiry of physiological regulation. He introduced many fundamental concepts regarding short and long time regulation of the circulation and its connection with the regulation of circulating volume, osmolarity and ionic composition of bodily fluids. He worked up a great many original experimental procedures – for instance, he was the first one to measure the value of pressure in the interstitial fluid. However, he was not only an innovative experimenter, but also a brilliant analyst and creative synthesizer. He was able to draw out new conclusions for the dynamics of processes in the body from the experimental

results and thus explain the physiological basis of a number of regulatory processes in the organism as a whole. Guyton's research has shown, for example, that it is not only the heart as a pump that controls the cardiac output; but that an equally important roles are played by the regulation of tissue perfusion, dependent on the oxygen supply, as well as on the filling of the vessels and the compliance of great veins. It was A.C. Guyton who proved that the long-term regulation of blood pressure is done by kidneys [9].

When you study the dynamism of regulatory processes, verbal description and common sense are often not sufficient. Prof. Guyton realized this 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 the 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 he graduated from Harvard University in 1943, he began his surgical internship at Massachusetts General Hospital. His surgical carrier was interrupted by war. He was called into the 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 had bound him either to a wheelchair or crutches for the rest of his life. However, his creative spirit did not leave him in this period of hardship, and he 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 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 Harvard University, he returned back to his hometown Oxford, Mississippi, where he first taught pharmacology at a two-year medical school; however, not long after that, he became head of the Department of Physiology at The University of Mississippi. He established a world famous physiological school in what used to be a rather provincial institute (on an 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 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 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] they used a 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, means of simulation development tools were used for graphic notation of the structure of physiological regulation relations, for example; Simulink by the 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.

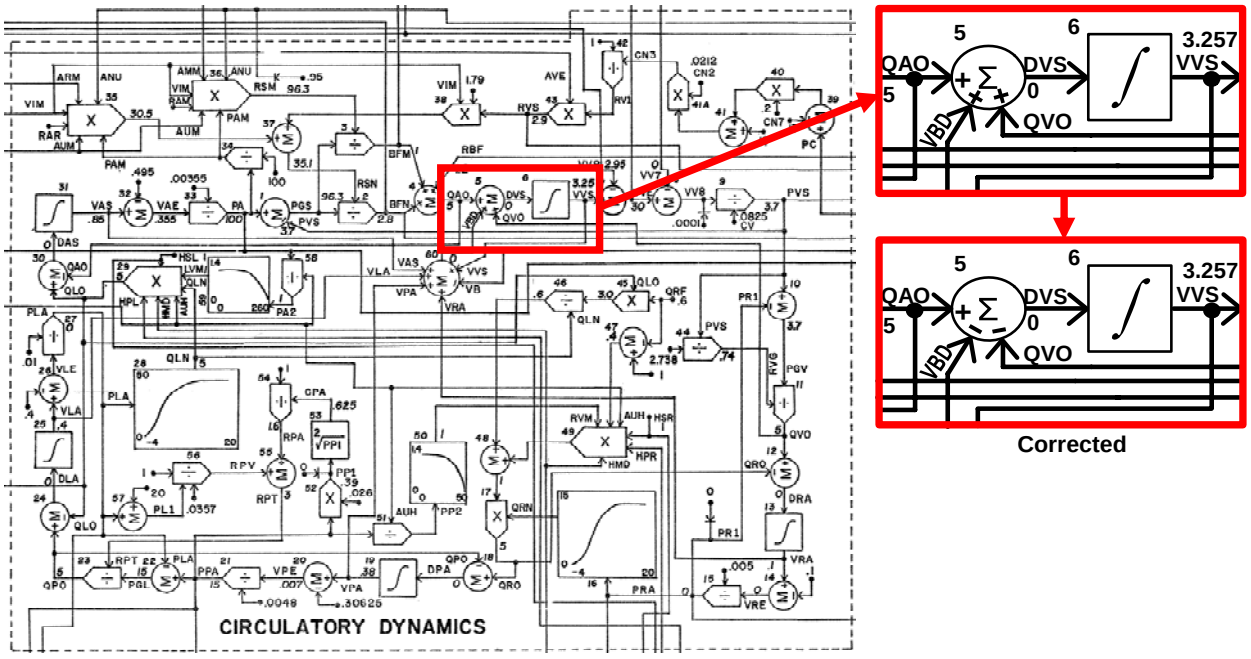

Figure 3: The error in the Circulatory Dynamics subsystem.

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, it does 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 up. The model either behaves inadequately or even becomes unstable, values start to oscillate and the model complex collapses. There were a few errors – changed signs, a multiplier instead of a divider, changed connection between blocks, missing decimal point, wrong initial conditions, etc. – but it was enough for a wrong functioning of the model. Being acquainted with physiology and system analysis, we could have avoided the mistakes with a little effort.

An 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 the right atrium (QVO). The rate change of filling of the 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.

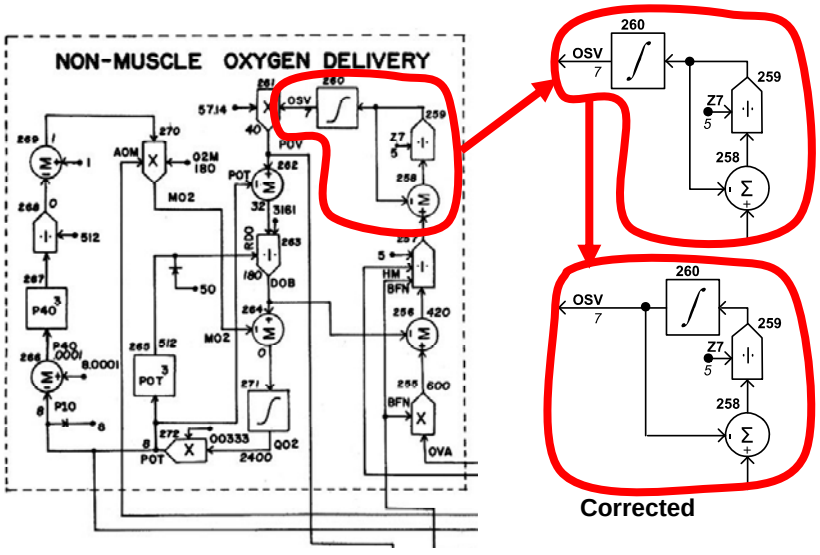

Figure 4: The error in the Non-Muscle Oxygen Delivery subsystem.

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

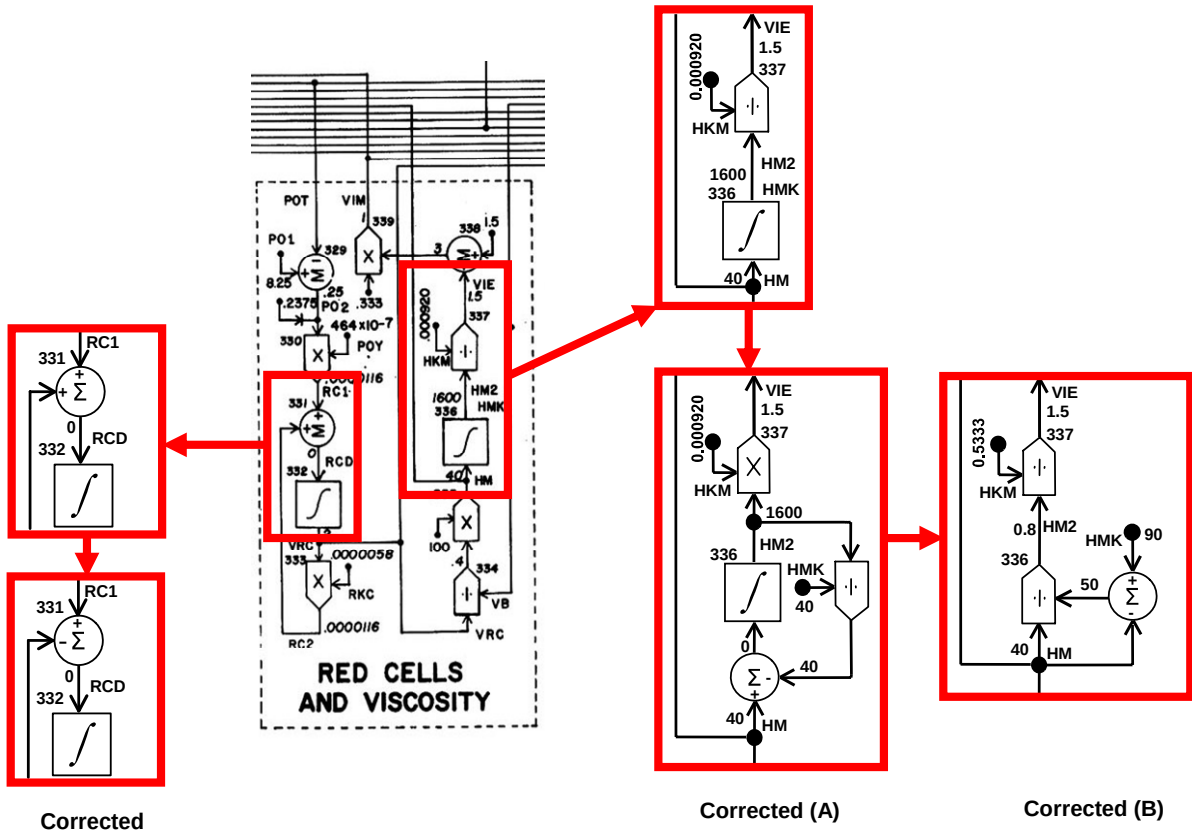

Figure 5: The errors in the Red Cells and Viscosity subsystem.

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 the value of OSV, and therefore it is sufficient to move feedback input to summator behind the integrator as it is indicated in the picture.

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 a portion of the 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 a stable situation and under normal conditions. If we divide this value by a constant parameter HKM (=0.000920), we should arrive at a 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 the correct calculation if we multiply the value HM2 by constant HKM instead of using division. Thus it is obvious, that block no. 337 should be a multiplier unit and not a dividing unit. In order to have the value of a variable HM2 in stable situation constant (and under normal conditions equal to value 1600), the input to integrator must have zero value (block no. 336). Therefore, it is apparent, that the depiction of feedback has been omitted in the diagram. The corrected diagram is shown in picture 6 as "Corrected (A)". Viscosity is proportionate to hematocrit and the integrator acts here as a dampening element. It can be from the experimental data that dependence of viscosity of blood on hematocrit is not linear proportionate [7]. Therefore in a later realization of the model (according to source text in Fortran language) the relation between hematocrit (HK) and portion of blood viscosity was caused by red blood cells (VIE) formulated as follows:

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

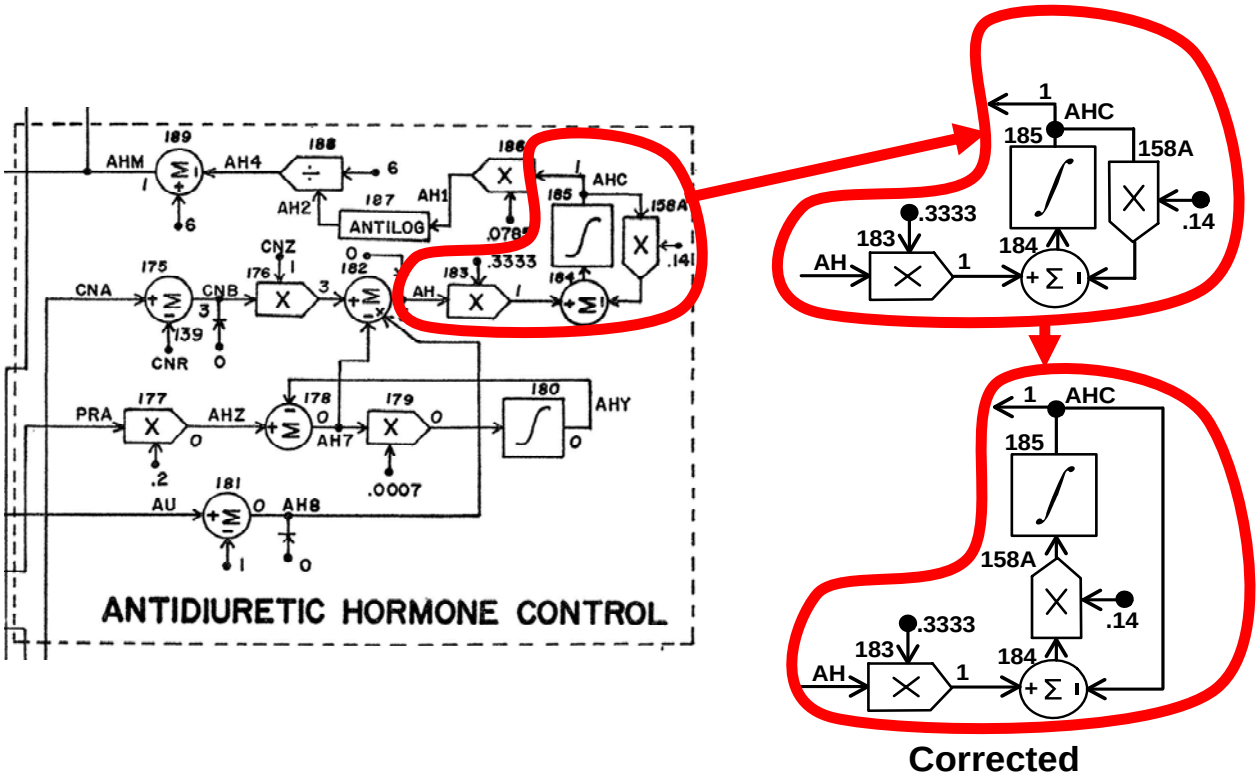

Figure 6: The error in the Antidiuretic Hormone Control subsystem.

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

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

$$0.333\,AH = 1,$$

$$AHC = 1.$$

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 a normalized concentration of this hormone (according to the norm). How is the normalized concentration of substance from normalized rate of substance creation calculated? The classic compartment approach will answer our question.

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

We come out of a simple compartment approach - into a whole-body compartment inflow the 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 the balance between inflow and outflow of the hormone.

$$F_i - F_o = \frac{dM}{dt} . \tag{2}$$

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

$$F_o = k\,c . \tag{3}$$

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

$$c = \frac{M}{V} . \tag{4}$$

Thus after inserting:

$$F_i - \frac{k\,M}{V} = \frac{dM}{dt} . \tag{5}$$

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

$$k_1 = \frac{k}{V} . \tag{6}$$

We arrive at:

$$F_i - k_1\,M = \frac{dM}{dt} . \tag{7}$$

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}:

$$c_0 = \frac{c}{c_{norm}} . \tag{8}$$

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}:

$$c_0 = \frac{c}{c_{norm}} = \frac{M}{M_{norm}} . \tag{9}$$

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

$$F_i = 1 ,$$

$$\frac{dM_{norm}}{dt} = 0 .$$

Therefore:

$$1 - k_1\,M_{norm} = 0 . \tag{10}$$

Normal quantity of hormone M_{norm} will be:

$$M_{norm} = \frac{1}{k_1} . \tag{11}$$

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

$$c_0 = \frac{M}{M_{norm}} = k_1\,M . \tag{12}$$

Thus:

$$M = \frac{c_0}{k_1} . \tag{13}$$

After inserting into differential equation we arrive at:

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

i.e.:

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

Thus:

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

According to this equation, the normalized concentration of the hormone c_0 is calculated from the normalized inflow of the 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:

$$F_i = 0.3333\,AH. \tag{17}$$

The normalized concentration of the hormone is:

$$c_0 = AHC, \tag{18}$$

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:

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

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

Quoted examples of errors in the 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. What was incorrect was only the graphic depiction of the 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 – pictures 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 correct the errors – the ones who took the pain over the analysis of the model easily uncovered the diagrams mistakes, the ones who just wanted to 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 to just test the behaviour of the model, s/he did not have to program anything (at the most they had to routinely convert the Fortran program into other programming languages).

5 Results

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

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

In the Simulink model, we also used 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 the form of Simulink subsystems. The 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" – conductors with input data are connected to their individual input, and signals with information about the value of individual physiological quantities are distributed from their output “pins” to other “simulation chips”.

Models formulated through the network of "simulation chips" are also the appropriate tools for team collaboration between branches of study [13]. Such a chart is much more legible also for an experimental physiologist who does not have to understand the complicated mathematical structure of a computational network inside a "simulation chip", however s/he understands the structure and functions of physiological relations. S/he can study the behaviour of a model in individual simulation chips on virtual displays and oscilloscopes, which are standard components of the 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, s/he can imagine how the model has expanded in the past 14 years.

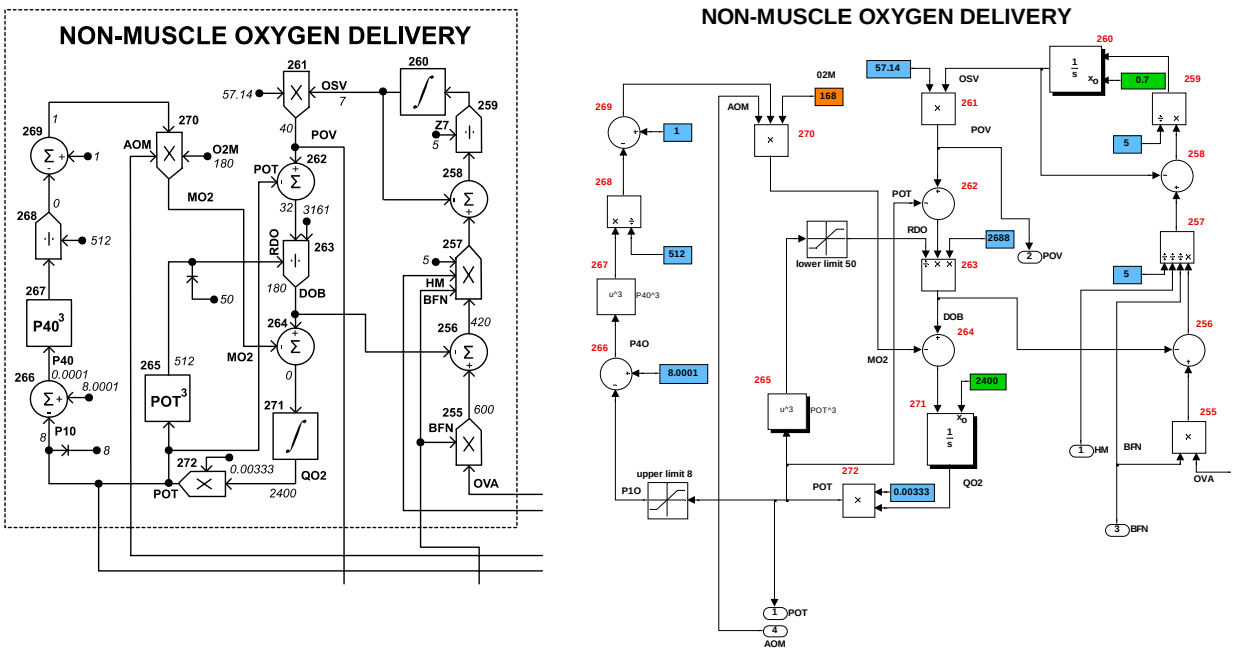

Figure 7: The pictorial block scheme of the original A.C.Guyton's model on the left and the model block diagram in the Simulink software tool. Analogically positioned and numbered blocks represent the same mathematical operations. Multipliers and dividers: blocks 255, 257, 259, 261, 263, 268 ,272, 270 ; sum blocks: 256, 258, 262, 264, 266, 269; integrator blocks: 260 a 271; function blocks (cubic function): 265 a 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.

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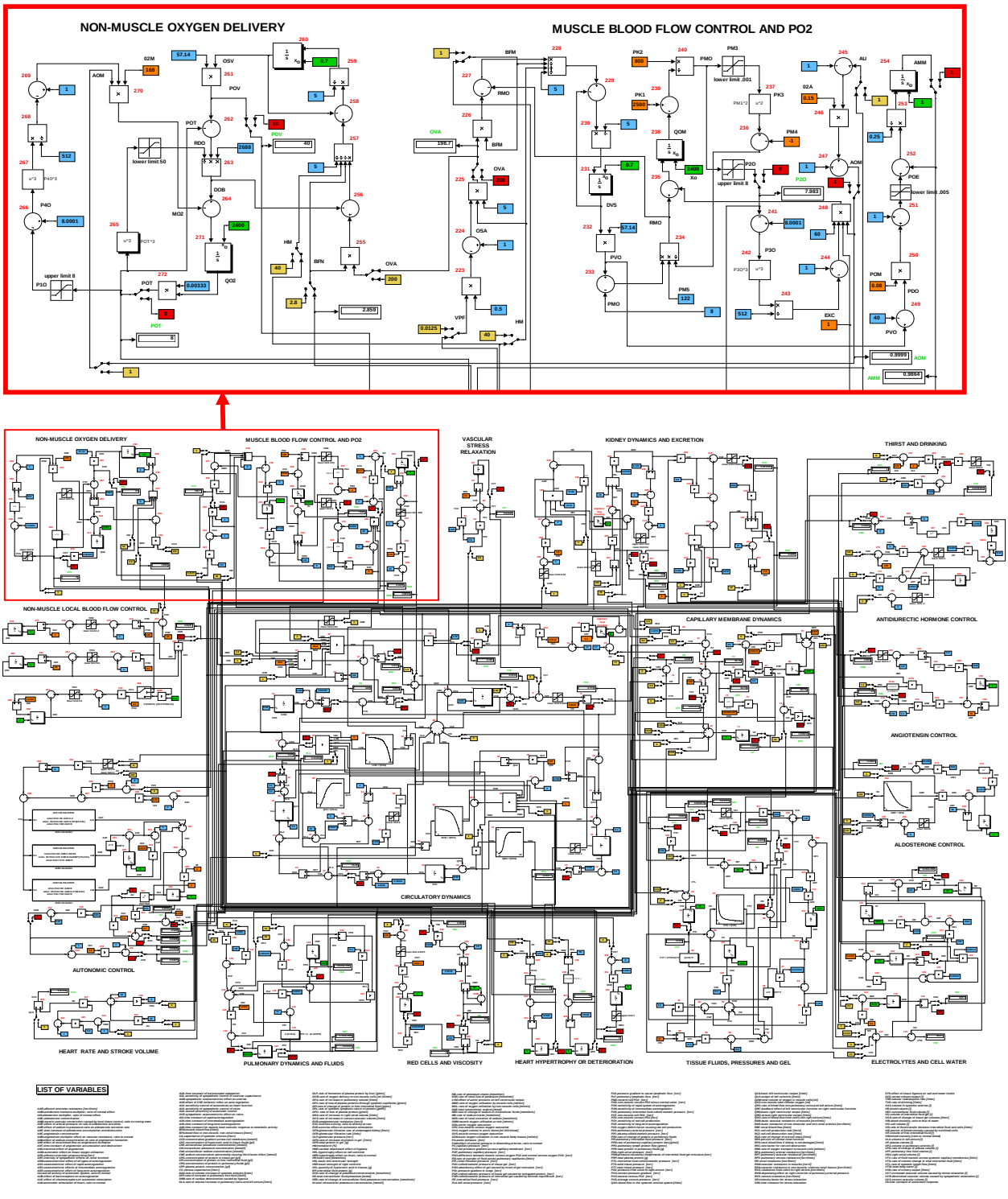

Figure 8: Guyton's overall regulation model of Circulation - implementation in Matlab/Simulink. The layout and block numbering is exactly the same as in the original Guyton's scheme (Fig. 2). The difference is, that this scheme is also a fully functional simulation model.

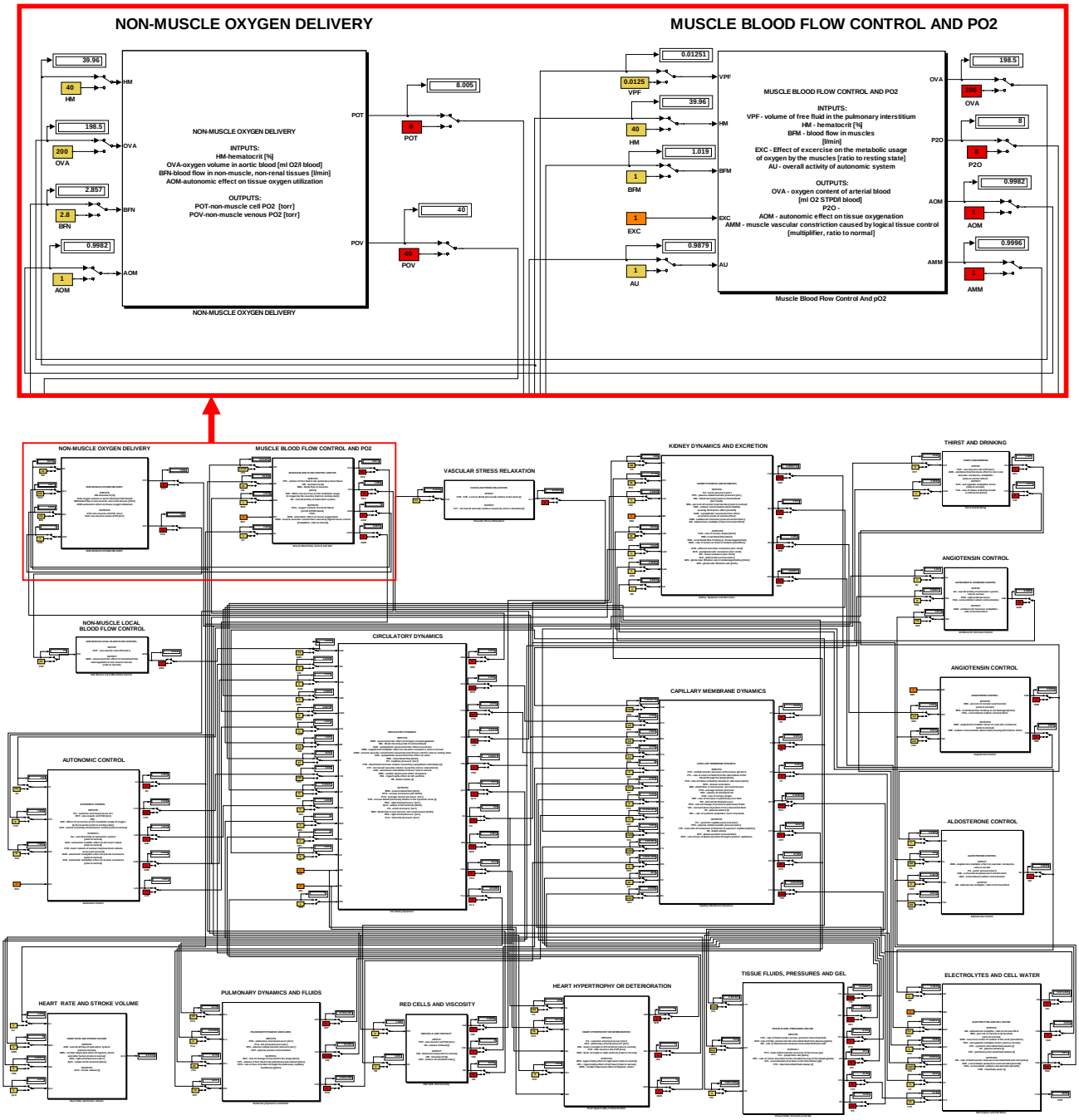

Figure 9: Guyton's overall regulation model of Circulation - implementation in Matlab/Simulink using Simulink subsystem blocks as "simulation chips".

Simulink implementation of the (corrected) Guyton's model made by us is available for download from the address http://physiome.cz/Guyton to anyone 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 time it is in the 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 the Czech Technical University (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 the Atlas of Physiology [18]. Unlike the book, these pictures can be interactive, and

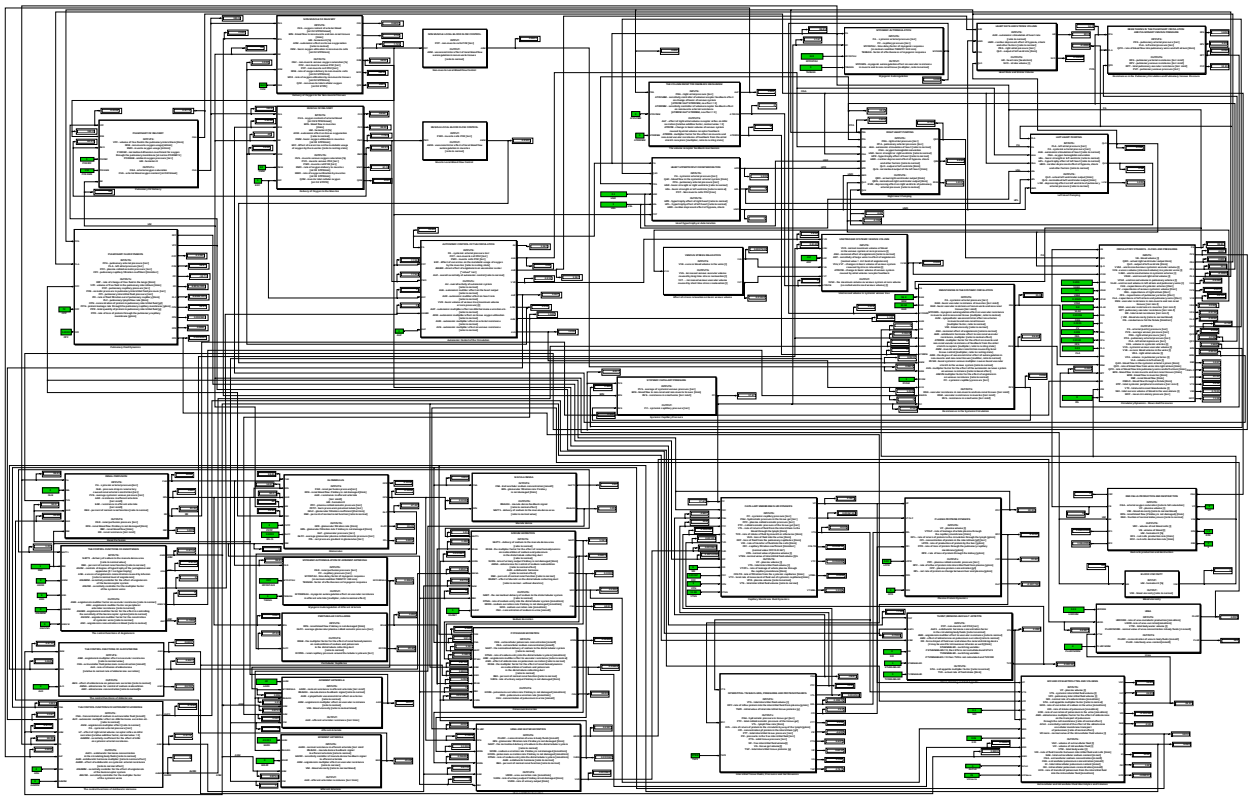

Fig 10. Simulink implementation of a Guyton-Coleman model from 1986.

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

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

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

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

During the creation of simulation models it is advantageous to use developmental tools designated for creating and identification of simulation models – for example Matlab/Simulink from the 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 the worldwide PHYSIOME project [3, 10].

Creating our 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). The future probably lies in simulators available on the web and on the 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 a PC. Moreover, today's technology allows us to add on a graphical attractive user-friendly interface to these models.

From the technological standpoint there are no obstacles that would prevent PCs from running learning simulators for practicing medical decision-making. The basis for a pilot's simulator during training pilots is the model of the plane. Similarly, one of the prerequisites when creating a medical simulator is the extensive simulation model of a human organism. This simulation model must include all significant physiological subsystems – circulation, respiration, kidney function, water, osmotic and electrolyte homeostasis, acid-base regulation, etc. – which have to be interconnected into the model. Therefore, now is the time of a renaissance in the formation of large integral models of human organism, and of the concept of integrative physiology, that Guyton 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 the legendary article by prof. Guyton from 1972 [6], together with Guyton's disciples, created a simulator Quantitative Human Physiology (QHP), whose theoretical basis is a new mathematical model of integrative human physiology which contains more than 4000 variables of biological interactions. A review edition of this simulator is freely available for download at http://physiology.umc.edu/themodelingworkshop/.

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

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

References

[1] S. R. Abram, Hodnett, B. L., Summers, R. L., Coleman, T. G., Hester R.L.: Quantitative Circulatory Physiology: An Integrative Mathematical Model of Human Physiology for medical education. *Advannced Physiology Education*, 31 (2), 202-210, 2007.

[2] N. M. Amosov, Palec B. L., Agapov, B. T., Jermakova, I. I., Ljabach E. G., Packina, S. A., Solovjev, V. P.: *Theoretical Research of Physiological Systems (in Russian)*. Kiev: Naukova Dumka, 1977

[3] J. B. Bassingthwaighte: Strategies for the Physiome Project. *Annals of Biomedical Engeneering* 28, 1043-1058, 2000

[4] T. G. Coleman, Randall, J. E.: HUMAN. A Comprehensive Physiological Model. *The Physiologist* 26, 15-21, 1982

[5] P. Fritzson: *Principles of Object-Oriented Modelling and Simulation with Modelica 2.1*, Wiley-IEEE Press, 2003

[6] A. C. Guyton, Coleman T. A. , & Grander H. J.: Circulation: Overall Regulation. Annual Review of Physiology, 41, 13-41, 1972.

[7] A. C. Guyton, Jones C. E., Coleman T. A.: *Circulatory Physiology: Cardiac Output and Its Regulation*. Philadelphia: WB Saunders Company, 1973

[8] A. C. Guyton, Taylor, A. E, Grander, H. J.: *Circulatory Physiology II: Dynamics and Control of the Body Fluids*. Philadelphia: WB Saunders Company, 1975.

[9] Guyton A. C.: The Suprising Kidney-Fluid Mechanism for Pressure Control – Its Infinite Gain!. *Hypertension,* 16, 725-730, 1990.

[10] P. J. Hunter, Robins, P., Noble D.: The IUPS Physiome Project. *Pflugers Archive-European Journal of Physiology*, 445,1–9, 2002.

[11] N. Ikeda, Marumo F. , Shirsataka M.: A Model of Overall Regulation of Body Fluids. *Annals of Biomedical Engeneering,* 7, 135-166, 1979.

[12] J. Kofránek, Anh Vu, L. D., Snášelová, H., Kerekeš, R., Velan, T.: GOLEM – Multimedia Simulator for Medical Education. In Patel, L., Rogers, R., Haux R. (Eds.). *MEDINFO 2001, Proceedings of the 10th World Congress on Medical Informatics*. London: IOS Press, 1042-1046, 2001, available at http://physiome.cz/Guyton.

[13] J. Kofránek, Andrlík, M., Kripner, T., Mašek, J.: From Simulation Chips to Biomedical Simulator. In Amborski K, Meuth H, (eds.): *Modelling and Simulation 2002, Germany 2002, Proceeding of 16th European Simulation Multiconference*, Germany, Darmstadt, 431-436, 2002, available at http://physiome.cz/Guyton.

[14] J. Kofránek, Andrlík M., Kripner T., Stodulka P.: From Art to Industry: Development of Biomedical Simulators. *The IPSI BgD Transactions on Advanced Research* 2. 62-67, 2005, available at http://physiome.cz/Guyton.

[15] J. Kofránek, Matoušek, S., Andrlík, M., Stodulka, P. Wünsch, Z. Privitzer, P., Hlaváček, J., Vacek O.: Atlas of Physiology - Internet Simulation Playground. In *Proceedings of EUROSIM 2007*, Ljubljana, Vol. 2. Full Papers (CD). (B. Zupanic, R. Karba, S. Blažič Eds.), University of Ljubljana, MO-2-P7-5, 1-9, 2007, available at http://physiome.cz/Guyton.

[16] J. A. Miller, Nair, R. S., Zhang, Z., Zhao, H.: JSIM: A JAVA-Based Simulation and Animation Environment, In *Proceedings of the 30th Annual Simulation Symposium*, *Atlanta, Georgia,* 31-42, 1997.

[17] G. M. Raymond, Butterworth E, Bassingthwaighte J. B.: JSIM: Free Software Package for Teaching Physiological Modeling and Research. *Experimental Biology* 280, 102-107, 2003.

[18] S. Silbernagl, Lang, F.: *Color Atlas of Pathophysiology*, Stuttgart: Thieme Verlag, 2000.

[19] P. Stodulka, Privitzer, P., Kofránek, J., Tribula, M., Vacek, O.: Development of WEB Accessible Medical Educational Simulators. In *Proceedings of EUROSIM 2007, Ljubljana*, Vol. 2. Full Papers (CD). (B. Zupanic, R. Karba, S. Blažič Eds.), University of Ljubljana, MO-3-P4-2, 1-6, 2007, available at http://physiome.cz/Guyton.

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