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ARTICLE

Milestones of the Modeling of Human Physiology

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ABSTRACT

An overview of about 70-year research efforts in area of mathematical modeling of human physiology is provided. The overview has two goals: (1) to recognize the main advantages and causes of disadvantages or disappointments; (2) to distinguish the most promising approach for creating future models. Until recently, efforts in the modeling of quantitative physiology were concentrated on the solving of three main types of tasks: (1) how to establish the input-output dynamic characteristics of a given isolated organ or isolated anatomical-functional system (AFS); (2) how to create a computer-based simulator of physiological complex systems (PCM) containing many organs and AFSs; and (3) how to create multi-scale models capable of simulating and explaining causalities in organs, AFSs, PCMs, and in the entire organism in terms that will allow using such models for simulating pathological scenarios (the "Physiome" project) too. The critical analysis of the modeling experience and recent physiological concepts convinced us that the platform provided by the paradigm of physiological super-systems (PPS) looks like the most promising platform for further modeling. PPS causally combines activities of specific intracellular mechanisms (self-tunable but of limited capacities) with their extracellular enhancers. The enhancement appears due to the increase of nutrients incomes toward cells affected because of low energy and inadequate chemical composition of cytoplasm. Every enhancer has its activator chemicals released by the affected cells. In fact, PPS, indicating causal relationships between cell-scale and upper-scales (in organs, AFSs, PCMs) physiological activities, is the single platform for future models. They must definitely describe when and how the bottom-to-up information flows do appear and how is the organism-scale adaptation activated against destructive trends in cells.

1. Introduction

In traditional human and animal physiology, mathematical methods for a long time were associated and mainly limited by statistics and regression analysis. However, since the middle of the XX Century, researchers who were initially educated in mathematics, physics, engineering or cybernetics, started to collaborate with biologists, widened the opportunities for analyzing life events and living systems. In particular, the adjoined researchers started to apply their professional knowledge and skills to assist in solving of certain actual problems in human physiology and medicine. Over time, one group of

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these assistants, who would not change their initial specialization, again switched-out to solving other problems not related to biology. Others, on the contrary, began to go so deep into biology, in particular, into physiology, that they began capable to clarify the existent biological concepts or even independently propose new concepts that in turn became the object of mathematical modeling and verifying. In parallel with the increased computers' power, and with the advent of new computing technologies for visualizing complex dynamic processes of life, these neo-physiologists became independent researchers capable of self-working on the creation of theoretical human physiology. Certainly, concepts concerning mathematical modeling of physiological events, objects, and systems also have been evolved. Currently, there is none human organ or anatomical-functional system (AFS) that's function is not formally described yet and investigated via computer simulations. Currently, publications on different aspects of these investigations exceed tens of thousands of articles, thousands of dissertations and monographs. The purpose of this article is not to review all of these publications: it is simply impossible. Readers interested in modeling methods and specifics of concrete models can independently find the necessary information in thematic reviews.

The goals of this short review article are (1) in outlining of the main milestones and approaches to modeling of human physiology, and (2) in highlighting the most promising ways for creating of models that could simulate the human integrative physiology on a basis of main rules evolutionary saved in a community of specialized cells.

2. A Brief Prehistory

The phenomenon of life was of interest not only to thinkers of antiquity and natural philosophers of the seventeenth and eighteenth centuries. In the 1870-s, Claude Bernard suggested the physical-chemical state of the internal liquid environment of the body to be almost constancy. These conjectures were strictly experimentally substantiated by Walter Cannon in 1929 when he formulated his concept of homeostasis [1]. Cannon's achievements intensified the common interest to life phenomenon. The mathematician Norbert Wiener, who collaborated with the physiologist Arturo Rosenblueth, and not only published a joint article with him on the processes of excitation in the heart muscle [2], but also, using Cannon's idea of the stabilizing role of negative feedback, he created a new science - cybernetics [3]. Some earlier, the famous physicist, one of the creators of quantum mechanics, Erwin Schrödinger published a book in which he tried to explain life from the point of view of a physicist [4]. Two questions he formulated concerned the basis of life - why biological molecules have to be permanently synthesized and why life needs enormously high energy expenditures. Namely, later by answering these questions, biochemists gave physiologists a new key for explaining the fundamental causalities between energy support and physiology. Now we realize that the emergence of special mechanisms (we call them physiological mechanisms), using the outside energy for the organization of cyclic transformations against natural gradients, had supported the physics and chemistry to origin the life phenomenon.

Although these scientists could not solve all the problems of biology, we should consider them as first modelers of the life phenomena: they have had looked at life from novel perspectives and their ideas and research methodology were further developed in unexpected directions.

3. A Brief History of Human Physiology Modeling Approaches

Cybernetics streamlined both design and the mathematical methods of calculation of stable technical dynamic systems. By the beginning of the 1950-s, the interest of cybernetics-mathematicians in the phenomenon of life received a methodologically new research impulse. Its initiator was Fred Grodins [5-6], for the first time tried to use the methodology of the control theory for a mathematical synthesis of human cardiovascular and respiratory quantitative physiology.

Looking at the history of physiological objects' and processes' modeling from a *bird's-eye view*, we can distinguish three main phases each with its characteristic signs.

At the initial stage, which started in the middle 50-s and continued up to the 90-s of the XX Century, modelers have seen their main role in formalizing accumulated empirical data. As the data basis mainly concerned physiology of isolated organs (heart, kidneys, liver, and pancreas) or anatomical-functional systems (AFS) like the cardiovascular system (CVS) and the respiratory system (RS), these systems were first formalized [5-15]. The formalization, spirited by the theories of the cybernetics and automatic systems, was aimed to present the functioning of both CVS and RS in cybernetic terms. Internal structural nuances and their likely consequences on the functionality of the original object had not been considered. The object had been looked like a "black-box" that within the given time interval τ (observation time) has its input variables $X(x_1(t)\ x_2(t),...,x_m(t)$, output variables $Y(y_1(t)\ y_2(t),...,y_n(t)$, and internal constants

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$K(k_1, k_2, ..., k_p)$. In the frame of this formalization, the function $Z(K,t)$ calculated as:

$$Z(K,t) = \frac{Y(y_1(t), y_2(t), ..., y_n(t); k_1, k_2, ..., k_p)}{X(x_1(t), x_2(t), ..., x_m(t))} \quad (1)$$

is a transfer function of the modeled object. Quantitative investigations of $Z(K,t)$ for certain test-situations (for variations of $x_1(t)$, $x_2(t), ..., x_m(t)$; $y_1(t)$, $y_2(t), ..., y_n(t)$; and\or $k_1, k_2, ..., k_p$) allowed the modeler to obtain additional calculated data capable to give the physiologist-empiricist additional information about object's properties.

In the sixteenths and seventeenths of the XX Century, one of the main physiological problems was a problem how to determine the goal functions of physiological systems (CVS, RS, or others) [15-17]. Moreover, echoes of this problem have not calmed down to this day too [18-22]. In this regard CVS is an illustrative object to demonstrate the novelty of the cybernetic analysis.

CVS provides organism by two variables - cardiac output (CO) and arterial pressure (AP). According to cardiovascular mechanics, the mean arterial pressure (MAP) better characterizes the hemodynamic laws than AP which is displaying cyclic variations. Therefore, experts often operate with MAP than with AP.

Physiologists discussed whether CO or MAP is the main goal function of CVS. Most experts suggested the homeostasis of MAP, provided by baroreceptor reflexes, to be the main goal function of CVS [18-23]. However, empirical data illustrated many situations in which MAP-level is floating [24-27]. One of actual problem was associated with hypertension [27-30]. According to spread concept, the altered sensitivity of MAP's control mechanisms is an initiator of hypertension thus certain theoretical research was focused on searching of quantitative approaches capable of measuring or calculating this sensitivity.

The cybernetic concept considers CVS to be a dynamic closed system (CS) built of two open systems (OS): an uncontrolled object (UO) and a regulator systems (RS). In fact, OS is the heart and vasculature filled by a summary blood volume and possessing by certain constant parameters. The function of RS is to alter these constants depending on input information came from multiple sensors. In short time intervals, arterial baroreceptors were commonly suggested to be the main sensors thus the arterial baroreflex is considered to be the main RS of MAP [13,16,21,26]. In long-time intervals, RS includes all physiological mechanisms capable of altering the hemodynamics. As the latter also depends upon summary blood volume that is under influences of multiple mechanisms and factors not relating to CVS, this simplified presentation is not to be adequate. Nevertheless, using the cybernetic approach, investigators have had calculated the values of gains for both physiological and hypertensive conditions [14-16].

Another approach to clinical use of calculated gains (sensitivity coefficients) was focused on assessing of the baroreflex servo-mechanism via its ability to change UO's parameters. As the heart rate ($F(t)$) is the most easy measurable parameter, the approach can be illustrated using $F(t)$. It is necessary to have at least two pairs of values of both MAP and heart rate: one - in an initial state of organisms, the second - after application of a standard procedure causing alteration of $F(t)$. For our convenience, let us denote MAP as P_A. Then $\Delta P_A = P_{A2} - P_{A1}$ and $\Delta F = F_2 - F_1$. The sensitivity of the heart rate to changes of MAP is: $S_F = \Delta F / \Delta P$. It is not hard to see that this approach requires all other influences on MAP and heart rate to be constant. However, evolution has saved a lot of multi-scale mechanisms simultaneously altering both these variables. Thus within the interval $F_{\min} \le F(t) \le F_{\max}$ real $F(t)$ should be calculated as:

$$F(t) = \begin{cases} F_{\min}, & \sum_{j=1}^{n} \Delta F_i^-(t) > F_a - F_{\min} \\ F_a + \Delta F(T) + \sum_{i=1}^{m} \Delta F_i^+(t) - \sum_{j=1}^{n} \Delta F_i^-(t), & F_{\min} \le F(t) \le F_{\max} \\ F_{\max}, & \sum_{i=1}^{m} \Delta F_i^+(t) + F_a > F_{\max} \end{cases} \quad (2)$$

where F_a is the heart rate under normal temperature (T), biochemical characteristics of blood, and biophysical characteristics of cells of sinus node, $\Delta F(T)$ is elevation of F_a with temperature increasing, $\Delta F_i^+(t)$ are accelerating effects of m mechanisms and $\Delta F_j^-(t)$ are deccelerating effects of n mechanisms. Note, that each such mechanism has its power and developmental inertia.

There is a theoretical problem: is each mechanism, influencing HR, specific regulator of CVS or certain mechanisms do not have the necessary and sufficient signs to be considered as the regulator [31-33]. Indeed, the baroreceptor reflexes that have receptor organs, central neurons reacting to the receptor impulses, and *sympa-*

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thetic and *vagus* nerves for controlling the activity of sinus node pacemakers, form a closed negative feedback nervous-reflector loop. However, a lot of blood chemicals influencing $\Delta F_i^+(t)$ or $\Delta F_i^-(t)$, have not their own feedback loops. By the way, this note also concerns multiple mechanisms generally activating or suppressing CVS via humoral channels [34]. The last factor is one of causes forcing physiologists to think that certain chemical agents like angiotensin, vasopressin, NO, CO2, SO2, despite having real pressor or depressor effects, are sooner sources for the appearing hypertension or hypotonic state than regulators of MAP-level. Real CVS is not an isolated system as it is assumed in the most models of hemodynamics. CVS interacts with multiple organs and AFS. In particular, total blood volume ($V_S(t)$), that is the main modifier of both central venous pressure and MAP, only in very little values of the observation time τ can be considered to be constant. Modifiers of $V_S(t)$ are acting via changing the liquid intakes from the digestive system ($q_w(t)$), of the diuresis ($q_d(t)$), expirations in lungs and skin. So, these effectors obviously do not belong to CVS.

$$\frac{dV_S}{dt} = q_w(t) - q_d(t) - q_{es}(t) - q_{ee}(t) - q_{cf}(t) + C_{be}(t) + C_{bl}(t) \tag{3}$$

where $q_{cf}(t)$ - trans-capillary flows, $q_{es}(t)$ - the evaporation with sweat, $q_{ee}(t)$ - expiratory fumes, $C_{be}(t)$ - blood salt concentrations, $C_{bl}(t)$ - concentrations of blood lipids.

In addition, MAP-level is also under influences of vessels' rigidity ($D(t)$) and unstressed volume ($U(t)$). However, neither $D(t)$ nor $U(t)$ can be directly measured: at organism-scale, they are still virtual characteristics. Nevertheless, they are important for modeling, especially in models with lumped parameters [7-10,12,36,37]. Formally,

$$D(t) = D0 + \sum_{i=1}^{m1} \Delta D_i(t); \quad U(t) = U0 - \sum_{i=1}^{m1} \Delta D_i(t), \tag{4}$$

where $m1$ is the number of vascular region, $D0, U0$ represent the initial values of $D(t)$ and $U(t)$.

The considerations above, formally presented in (2)-(4), are not the exclusive problems arose during use the model-based methods in clinics. As a rule, the function $Z(K,t)$ for an organ or even for a receptor is non-stationary and has a non-linear form. In case of a multi-fiber aortic nerve, the non-linear impulses-pressure curve looks like S-shaped [38,39]. For correct calculations of gains one needs to use complex calculus. The problem is facilitated by the fact that in the field of normal physiological quantities of $x_1(t)\ x_2(t),...,x_m(t)$; $y_1(t)\ y_2(t),...,y_n(t)$, and $k_1, k_2,..., k_p$, the non-linearity can be ignored and linear dependencies used. In the simplest case, when $m = 1$ instead of the dynamic $Z(K,t)$ one can use a simple output-input ratio.

Modelers try to approximate empirically obtained nonlinear curves by piecewise linear ones. Though such substitutions often are not incorrect they do not reveal and take into account one important internal cause of the nonlinearity. The matter is that the nonlinearity usually is an effect appearing when one sums a lot of discrete results that are reactions of individual components (receptors, common type cells) forming a population [34]. In fact, elements of such populations rarely are absolutely identical. Normally, they have slight structural differences (anisotropies). So, changes in the statistical distributions of elements possessing by the same anisotropy altering the graph form of $Z(K,t)$.As these ultra-structural alterations are the first signs of pathological trends, the substitution of the dynamic $Z(K,t)$ by the simple output-input ratio hides these early pathological trends.

In (1), we considered $k_1, k_2,..., k_p$ to be independent of time. However, this assumption is not correct forever. In some organs (for example, in heart) certain $k_1, k_2,..., k_p$ are constant in the models that describe static input-output relations and variables if the model does simulate the dynamic events within the cardiac cycle. Thus in the latter case, the myocardium elastance, valves' resistance are included with approximations of their dynamics [40-44].

The cybernetic concept and calculations of the simplified version of the gain also were used during the analysis of more complex RSs like the renal control of MAP through the renin-angiotensin-aldosterone loops (see review [45]). However, there is an additional reason to estimate such theoretic models as those that creating incorrect physiological understanding of negative feedbacks. The matter is that cybernetics use a virtual notion known as "set-point". The cybernetic mechanism stabilizing the value of $Y(y_1(t)\ y_2(t),...,y_n(t)$ despite certain alterations of $X(x_1(t)\ x_2(t),...,x_m(t)$ is based on a comparison of the current value of $Y(t)$

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with a given value of Y_0 (namely, the "set-point"). A difference $\varepsilon = Y_0 - Y(t)$ is a signal that goes to the gears forming a correction influence added to the input variable $X(x_1(t)\ x_2(t),...,x_m(t)$. However, real neuronal structures providing the "set-point" have not been identified yet. So, reasonable is to state that biological homeostatic mechanisms will have another organizing principle. The reciprocally acting physiological mechanisms are the most likely pretenders of this role [34].

Perhaps, the reasons and examples described above are sufficient to state that already at the first phase of modeling, in several models most organs, instead of the "black-box", were already transformed into a "gray-box" in which certain physiological rules were already clarified and formalized. Certainly, this widened model's usability. At the same time, a lot of difficulties and problems appeared. Some of them practically disappeared with the beginning of modeling's second phase that began due to appearing of powerful personal computers. A little by little, new mathematical methods and software, had provided modelers by high-speed computing and advanced visualization technologies. So, modelers became aware of creating models containing more and more detailed physiological nuances.

During1980-s and early 1990-s, traditional physiology has essentially modified due to penetrated methods of molecular analysis. Therefore, the advanced versions of models increasingly included descriptions of the molecular basis of certain physiological mechanisms. However, already in the middle of 1990-s, both modelers and potential users met new problems: (1) how to compare simulation results of different versions of the one and the same organ's model; (2) how to estimate model's correctness; (3) how long the necessity of new model creation will last yet, and at last (4) is it possible to unify human physiology models?

The "Physiome" long-term project opened the third phase of modeling and lasting currently was the general answer to these questions.

The "Physiome" Ideology and Research

The "Physiome" project was inspired by the well-known "Genome" project. The International Union of Physiological Sciences (IUPS) launched the Physiome Project at the IUPS World Congress in St Petersburg in 1997 [46]. Apologists of a novel research ideology aimed to bring quantitative bioengineering approaches to the study of anatomy and physiology. Both physiologists and modelers assumed that the model of human physiology must incorporate all scientific data concerning genetic, molecular, intracellular, multicellular events, organs' functionalities, and at last integrative organism-scale physiology. It also was declared every model to be strongly verified using empirical data. In the frame of the project, to support it by powerful techniques and technologies, both creation of special software and data centers for an accumulation of both initial biological and simulation data was planned [http://www.iups.org/physiome-project/]. Financial support of the research and developments was organized in the frames of both international "Physiome" projects (http://www.iups.org/physiome-project/; http://physiomeproject.org/about/molecules-to-humankind; https://www.auckland.ac.nz/en/abi/our-research/research-groups-themes/physiome-project.html), and national "Physiome" projects (for example, [46-52]; (https://www.physiome.org/;https://www.physiome.org/Links/publications.html; https://www.researchgate.net/publication/312381514_HD_Physiology_Project-Japanese_efforts_to_promote_multilevel_integrative_systems_biology_and_physiome_research.

Over the past two decades, in the development of models, the ideology of the Physiome has become to be dominant. Many models of particular physiological mechanisms that function on different spatial scales have been created (for example, [53-57]. We cannot provide here for their detailed and comparative analysis. We only note that each such model is a huge work of its creators, which includes not only complex mathematics and simulation technologies, but also a rigorous justification of the assumptions forced to made and the limitations resulting from them. As a rule, most models were created with a direct or remote applied purpose. Some of them are relatively simple, while the model [56], designed to simulate the main effects of a combination of physiological and artificial mechanisms protecting humans against loss of vision or consciousness in conditions of extreme pilotage accelerations, contains more than 2000 differential equations. Since none of the Earth-based physical models is adequate, separate models (for example [57,58]) were developed to test existing hypotheses regarding the processes of the organism's adaptation to zero-gravity conditions.

To our opinion, at least in the aspect of the multi-scale physiology, the "Physiome" ideology met unsolvable problems. Some of them are discussed below.

4. Discussion

Physiology is a fundamental science that simultaneously is the theory of medicine. However, physiologists already released that their empirical research methods are too

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primitive to reveal the real complexity of the human organism. Models developed since the middle 1950-s use origin mixed reactions of traditional physiologists. On the one side, they need methodological support. On the other side, mainly because the mathematics and research technologies used by modelers are not comprehensively understood by physiologists, the latter feeling certain distrust in these models and the results. This distrust is also based on the fact that models use a lot of quantitative data that cannot be measured. In contrast, orders (users) of applied models use simulators to have certain presentations, namely about these un-measured living characteristics. Perhaps, this is why applied physiologists ordered the most computer simulators. It seems this reason is right also for the practical medicine needed to improve diagnostic and treat technologies via the creation of personalized computer models of pathologies. Namely, the medical needs forced to support large research projects like the "Physiome" project. However, to our opinion, models of complex physiological mechanisms are still very far from this medical ideal. Nevertheless, modeling efforts have to be supported because there is none acceptable alternative to how to reveal these mechanisms.

Only a little part of the models has been analyzed above. The analysis din not concern models of functional systems like the system of thermoregulation and the immune system. Certainly, models of both these systems also exist (for example, [59-62]).

Concerning the Reasonable Complexity of the Model

The model cannot take into account all the facts. If one creates a didactic model of certain organ or AFS, he/she are free to reduce the model until it simulates distinguish biological functionalities. Currently, a lot of depositaries accumulated free-usable didactic models of human physiology (https://caehealthcare.com/patient-simulation/pediasim/; https://physiology.kitware.com/; https://biogearsengine.com/; http://hummod.org/; http://simvascular.github.io/; https://simtk.org/projects/opensim/). Creators of other models always are searching for a reasonable compromise between the requirements of empiricists and technological constraints. In this sense, the famous model of circulation's overall control [45] is an exclusive one both by its enormous complexity and by the attempt to test several concepts and hypotheses concerning general human physiology. Studying this model was obligatory work for each modeler thus we should make several notations here.

First of all, the model was not strongly identified. Critics considered this a sufficient reason not to notice or downplay the model's merits. But the main author - Arthur Guyton was a very famous and well- recognized physiologist one to suggest that the quantitative relationships used in the model approximately do correspond to reality. It is worth to underlay that the model incorporated 16 organs and AFS influencing the parameters of CVS and determining both central and regional circulation. Many curves and constants reflecting the current state of each modeled unit were tunable. But authors have had not proposed a reasonable algorithm for automatically tuning: they did it in manual mode, based on their experiences. By the way, authors of another complex model [63], looked like the model of Guyton et al [13] model, were also forced to simulate physiological events in the rest condition or under the gradual exercise by altering constants in manual mode.

To our opinion, the model of Guyton et al [13] had one big aim - to make a theoretic analysis of complex physiological events as it is possible. However, such models also met specific problems concerned technologies of simulations. The model incorporated physiological mechanisms of essentially different dynamics. Some events go on within seconds while others, to show essential alterations, need hours or months. Neither mathematical methods nor computers' power was capable to provide simultaneous modeling. Thus, the authors tried to make partial simulations and then combine their results manually. Despite modern computers exceeding the power of computers of XX Century thousand times, currently, the simultaneously modeling of multi-scale biological transformations is still an actual problem and nowadays.Shim et al [64] have developed a comprehensive cell model that simulates the sequential cellular events from membrane excitation to contraction in the human ventricle. By combining this ventricular cell model with a lumped circulation model, they examined how blood pressure dynamics in the ventricle and aorta are related to the cellular processes. However, to convert cell contraction into ventricular pressure authors have used Laplace's law, introducing a simple geometric model of a ventricle: one shaped like a thin-walled hemisphere. The time courses of the hemodynamic properties, as well as the volume-pressure trajectory of the left ventricle, were well reproduced. The multi-scale cardiovascular model, which covers from cardiac cells to the circulatory system, simulates the typical characteristics of heart mechanics, such as the pressure-volume relationship, stroke volume and the effect of the increased maximum free calcium concentration on cardiovascular hemodynamics. The variation due to different pacing frequencies for myocyte excitation was also investigated to assess the

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effects of heart rate on cardiac cells and the circulatory system.

To model real physiological mechanisms acting on a whole organism-scale, it is necessary to take into account the followings. First of all, the modeler needs a correct conceptual vision of the organs' interaction. Second, he\she should take into account mechanisms providing the self-adaptiveness of the cell. Third, it also is necessary a conceptual vision of mechanisms-enhancers that are activating when the cell-scale mechanisms are not capable of lonely provide cell survival. This triad duly understood should be transferred into a technology in which the cell-scale events are the primary ones while every next-scales' mechanisms represent assistant mechanisms evolutionarily being saved because they enhance the cell capability to provide optimal-like metabolism. Namely, these ideas were proposed and argued in recent publications [31-34,65,66].

Even accepting this recommended ideology, the modeler should not ignore the effects of two other fundamental cell-scale facts. The first one concerns the rate of metabolism. Though its mean value is genetically predetermined in each cell type, the metabolic rate is essentially varying in different phases of the cell cycle. In addition, the duration of every phase is not stable but depends upon material incomes. Therefore, special check-point mechanisms control whether products to be synthesized within the current phase are already present. The second effect mostly expressed in exciting cells, appears because of influences that came from other cells. Namely, due to these stimulating or inhibiting influences, both the integrative physiology and behaviors are provided [34]. However, the integrating influences disrupt the normal course of metabolism, cause internal destruction in the target cell. Therefore, special mechanisms, which can be read in more detail in [31-34], activate mechanisms that serve the synthesis of ATP molecules. As many organs take part in obtaining, transforming, and delivering of source materials for the synthesis of ATP in a cell, they all together are considered functionally to be physiological super-systems (PS). Another PS is providing the chemical purity of the cytoplasm.

To realistically model physiological events in multicellular objects (in a cells' population, in organs built of multiple such populations, as well as in AFS, and PS), the modeler also should take into account dynamic effects caused by internal heterogeneities of cells into the cell population [65].

So, the multi-scale modeling, to be capable of realistically simulating both the normal physiological mechanisms and multiple scenarios leading to the abnormal working of these mechanisms, needs to be based on the recent concept explaining the metabolic and functional integrity of human specialized cells [34].

In the review [67], authors discussing research efforts to the whole-heart modeling. The models seems to be multi-scale are rather describing biophysical than physiological mechanisms. The same is true for the models like [69-71] while models described in [72-74] combine both physiological and biophysical mechanisms. The multi-scale model of the heart, described in [75], illustrates the effects provided by using massively parallel computers. It is undoubtedly that supercomputers opening new opportunities for simulations in physiology.

Clinical models we have not analyzed because they include a lot of nuances specific for each pathology but not principal in the frame of our overview.

It is worth to return to the questions first formulated by Schrödinger in [4] and described above. Three main answers are now known. Tertiary and quaternary macromolecules, which make up most of the biological structures of the cell, are sensitive to thermodynamic and other fluctuations. Therefore, a permanent compensatory synthesis of destroyed molecules takes place in the cell. Fluctuations also affect the throughput of the portal mechanisms of cell membranes, disrupting the resting potential of the cell. Their recovery is possible with the consumption of ATP. In addition to these reasons, in a multicellular organism of animals or humans, the integration of heterogeneous cells during the functioning of organs and systems also contributes to the additional energy expenditure [34]. Thus, it is impossible to correctly model physiological multi-scale processes and phenomena without properly describing the energy dependence of the simulated effects in these models. Since ATP is synthesized from the limited internal resources of carbohydrates and oxygen, in fact, these restrictions significantly modulate both organ and body physiology. So far, only the first attempts have been made to create an integrated model of the physiological megasystem providing the energy balance in each cell of the body [31-34,76]. We believe that this aspect of modeling should be further developed in future models of human physiology and pathophysiology.

5. Conclusion

Mathematical modeling now is a legal method of physiological research. Multiple quantitative models describe functions of human organs, anatomical-functional systems (AFS), and functional systems (FS) under norm and certain pathologies. Most models, operating with both measured data and virtual data or heuristics, give the physiologists-empiricists additional information and help them to better understand intimate mechanisms governing

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the living system. As the physiological concepts serve the basis of the models and specialized computer simulators, simulations cannot provide conclusions cardinally differing from the used concept. This is why nether principles or rules organizing and governing the human integrative physiology at rest and/or under behavioral activities have not been clarified yet by simulations. Moreover, even concepts used in most models of organs or AFSs suggest the organ or AFS have its physiological goals and mechanisms for their providing. In fact, at physiological levels of life organization, there is none special goal: it is an illusion born by mechanisms structurally-functionally linked in forms of special negative or positive feed-backs to supply cells by energy and materials in order that makes possible the entire chain to repetitively do biological works. Every mechanism combining reciprocally activating sub-mechanisms damps the extreme oscillations of life variables thus creating the illusion of the local goal. In order to comprehend the principles of such mechanisms at multiple scales, it is necessary to create novel mathematical models (NMM). Cellular self-regulators must be the basis of NMM. As every self-regulator possesses limited power, NMM also must contain models describing conditions for appearing/disappearing of special chemical agents that are penetrating into the blood and activating additional multi-cellular enhancers of intracellular self-regulators. As cells simultaneously fighting for common resources, the entire organism will be modeled as a net of physiological super-systems together supporting cells' optimal physiology. Only such models could simulate both short-term and long-term adaptive responses of the human organism to internal/external destructive challenges.

References

[1] Cannon WB. Organization for physiological homeostasis. Physiol. Rev., 1929, 9: 399-431.

[2] Wiener N., Rosenblueth A. The mathematical formulation of the problem of conduction of impulses in a network of connected excitable elements, specifically in cardiac muscle. Arch. Inst. Cardiologia de Mexico. 1946, XVI(3-4): 205-265.

[3] Wiener N. Cybernetics: Or Control and Communication in the Animal and the Machine. 1948, Technology Press.

[4] Schrodinger E. What is life? The Physical Aspect of the Living Cell. 1944, Cambridge University Press,

[5] Grodins FS, Gray JS, Schroeder KR, Norins AL, Jones RW. Respiratory responses to CO2 inhalation. A theoretical study of a nonlinear biological regulator. J Appl Physiol. 1954, 7(3): 283-308.

[6] Grodins F. Control Theory and Biological Systems. N. Y.: Columbia. Univ. Press, 1963.

[7] Beneken GW. Investigation on the regulatory system of the blood circulation. In: Circulatory Analog Computers. Amsterdam: North-Holland Publishing company, 1963: 16-28.

[8] Beneken GW. A mathematical approach to cardiovascularfunction. The uncontrolled human system. Drukkerij Elinknjk Utrecht, 1965.

[9] Defares YJ, Osborn JJ, Hara HH. Theoretical synthesis of the cardiovascular system. Acta Physiol, Pharmacol., -Neerl., 1962, 12: 189-265.

[10] De Pater L., van den Berg J.W. An Electrical Analogue of the Entire Human Circulatory System. Medical Electronics and Biological Engineering, 1964, 11: 161-166.

[11] Scher AM, Young AC. Servoanalysis of carotid sinus effects on peripheral resistance. Circ. Res., 1963, 12: 152-162.

[12] Defares Y.J. Examples of cardiovascular models simulation of the cardiovascular system. J. Chron. Dis., 1966, 19: 401-410.

[13] Guyton AC, Coleman TG, Granger HJ. Circulation. Overall Regulation. Annual Review of Physiology, 1972, 34: 13-46.

[14] Sagawa K. Comparative models of overall circulatory mechanics. In: Brown JHV, Dikson JP Advances in Bio-med. Eng. Academ. Press. New York, London, 1973, 3: 1-96.

[15] Sagawa K. Concerning "gain". Am J Physiol., 1978, 235(2): H117.

[16] Guyton AC. Renal servo-control of arterial blood pressure. J. Appl. Physiol, 1967, 22: 139-142.

[17] Guyton AC. Long-term arterial pressure control: an analysis from animal experiments and ... in the pathogenesis of hypertension, N Engl J Med., 1966, 356: 2007.

[18] Osborn JW, Jacob F, Guzman P. A neural set point for the long-term control of arterial pressure: beyond the arterial baroreceptor reflex. Am J Physiol Regul Integr Comp Physiol. 2005, 288(4): R846-855.

[19] Brands MW. Chronic blood pressure control. Compr Physiol. 2012, 2(4): 2481-2494.

[20] Dorrington KL, Pandit JJ. The obligatory role of the kidney in long-term arterial blood pressure control: extending Guyton's model of the circulation. Anaesthesia., 2009, 64(11): 1218-1228.

[21] Nishida Y, Tandai-Hiruma, M, Kemuriyama, T. et al. Long-term blood pressure control: is there a set-point in the brain?. J Physiol Sci. 2012, 62: 147-161. https://doi.org/10.1007/s12576-012-0192-0

[22] BensonJF, SchoemanJP, VenterFJ, Ker JA, ZeilerGE, Bester L, van Niekerk J, Tintinger

DOI: https://doi.org/10.30564/jhp.v2i1.1905

GR. Aortic Arch Baroreceptor Stimulation in an Experimental Goat Model: A Novel Method to Lower Blood Pressure Front. Cardiovasc. Med., 2019. https://doi.org/10.3389/fcvm.2018.00193

[23] Burgoyne S, Georgakopoulos D, Belenkie I, Tyberg JV. Systemic vascular effects of acute electrical baroreflex stimulation. AJP Hear Circ Physiol. 2014, 307:H236-241. DOI: 10.1152/ajpheart.00422.2013

[24] Hori D, Max L, Laflam A, Brown C, Neufeld KJ, Adachi H, Sciortino C, Conte JV, Cameron DE, Hogue CW Jr, Mandal K. Blood Pressure Deviations From Optimal Mean Arterial Pressure During Cardiac Surgery Measured With a Novel Monitor of Cerebral Blood Flow and Risk for Perioperative Delirium: A Pilot Study. J Cardiothorac Vasc Anesth. 2016, 30(3): 606-612. DOI: 10.1053/j.jvca.2016.01.012

[25] Höcht C. Blood Pressure Variability: Prognostic Value and Therapeutic Implications. International Scholarly Research Notices, Notices, 2013. https://doi.org/10.5402/2013/398485

[26] Raven PB, Chapleau MW. Blood pressure regulation: overview and future research directions. Eur J Appl Physiol. 2014, 114(3): 579-586. DOI: 10.1007/s00421-014-2823-z

[27] Nishi EE, Bergamaschi CT, Campos RR. The crosstalk between the kidney and the central nervous system: the role of renal nerves in blood pressure regulation. Exp Physiol. 2015, 100(5): 479-484. DOI: 10.1113/expphysiol.2014.079889

[28] Averina VA, Othmer HG, Fink GD, Osborn JW. A new conceptual paradigm for the haemodynamics of salt-sensitive hypertension: a mathematical modelling approach. J Physiol. 2012, 590(23): 5975-5992.

[29] Bolívar JJ. Essential Hypertension: An Approach to Its Etiology and Neurogenic Pathophysiology. Int J Hypertens. 2013. DOI: 10.1155/2013/547809

[30] Ivy JR, Bailey MA. Pressure natriuresis and the renal control of arterial blood pressure. J Physiol. 2014, 15, 592(18): 3955-67. DOI: 10.1113/jphysiol.2014.271676

[31] Grygoryan R.D. Comprehension of individual adaptation mechanisms: endogenous tuning of constants determining optimal physiological states. Slovak international scientific journal, 2019, 32: 67-72.

[32] Grygoryan R.D., Sagach V.F. The concept of physiological supersystems: New stage of integrative physiology. Intern. J. of Physiol. and Pathophysiology, 2018, 9(2): 169-180.

[33] Grygoryan RD. Endogenous variators of individual health corridor. Znanstvena misel journal, 2019, 35: 31-37.

[34] Grygoryan RD. The Optimal Coexistence of Cells: How Could Human Cells Create The Integrative Physiology. Journal of Human Physiology.2019, 1 (01):8-28. DOI: 10.30564/jhp.v1i1.1386

[35] Kokalari I. Review on lumped parameter method for modeling the blood flow in systemic arteries. Journal of Biomedical Science and Engineering 2013, 06(01): 92-99. DOI: 10.4236/jbise.2013.61012

[36] Shimizu S. Une D, KawadaT, HayamaY, KamiyaA, Shishido T, Sugimachi T. Lumped parameter model for hemodynamic simulation of congenital heart diseases The Journal of Physiological Sciences, 2018, 68: 103-111. https://doi.org/10.1007/s12576-017-0585-1.

[37] Corsini C, Baker C, Kung E, Schievano S, Arbia G, Baretta A, Biglino G, Migliavacca F, Dubini G, Pennati G, Marsden A, Vignon-Clementel I, Taylor A, Hsia TY, Dorfman A. Modeling of Congenital Hearts Alliance (MOCHA) Investigators: An integrated approach to patient-specifc predictive modeling for single ventricle heart palliation. Comput Methods Biomech Biomed Engin., 2014, 17: 1572-1589.

[38] Dampney RAL. Resetting of the Baroreflex Control of Sympathetic Vasomotor Activity during Natural Behaviors: Description and Conceptual Model of Central Mechanisms. Front Neurosci., 2017, 11: 461. Published 2017. DOI: 10.3389/fnins.2017.00461

[39] Wallin BG, Charkoudian N. Sympathetic neural control of integrated cardiovascular function: insights from measurement of human sympathetic nerve activity. Muscle Nerve. 2007, 36(5): 595-614.

[40] Pope SR, Ellwein L, Zapata EC, Novak V., Kelley CT, Olufsen MS. Estimation and identification of parameters in a lumped cerebrovascular model, Mathematical Biosciences and Engineering 2009, 6(1): 93-115.

[41] Rideout V. Mathematical and computer modeling of physiological systems, Prentice Hall, Englewood Cliffs, NJ, 1991.

[42] Sunagawa K, Sagawa K. Models of ventricular contraction based on time-varying elastance, Critical Revies in Biomedical Engineering, 1982, 7(3): 193-228.

[43]Timischl S. A global model of the cardiovascular and respiratory system, Ph.D. thesis, University of Graz, Institute for Mathematics and Scientific Computing, 1998.

[44] Grygoryan RD, Degoda AG, Dzhurinsky EA, Khar-

 DOI: https://doi.org/10.30564/jhp.v2i1.1905

sun DS. A simulator of a pulsatile heart. Problrms in programming, 2017, 4: 98-108.
DOI: https://doi.org/10.15407/pp2017.04.098
[45] Cowley A. W., Jr. Long-term control of arterial blood pressure. Physiol Rev., 1992, 72: 231-300.
[46] The IUPS Physiome Project. http://www.iups.org/physiome-project/
[47] Hunter PJ, Viceconti M. The VPH-Physiome Project: Standards and Tools for Multiscale Modeling in Clinical Applications. 2009 IEEE Reviews in Biomedical Engineering, 2: 40-53. DOI: 10.1109/RBME.2009.2036204
[48] Bassingthwaighte JB and Chinn TM. Re-examining Michaelis-Menten enzyme kinetics for xanthine oxidase. Adv Physiol Educ, 2013, 37: 37-48.
[49] Bassingthwaighte JB, Butterworth E, Jardine B, Raymond G. Compartmental modeling in the analysis of biological systems. In: Computational Toxicology (Methods in Molecular Biology Series), edited by Brad Reisfeld and Arthur N Mayeno. New York NY: Springer Science+Business Media LLC, 2012, 929: 391-438.
[50] Bassingthwaighte JB, Beard DA, Carlson BE, Dash RK, Vinnakota K. Modeling to link regional myocardial work, metabolism and blood flows. Ann Biomed Eng. 2012, 40(11): 2379-98. DOI: 10.1007/s10439-012-0613-5
[51] Niederer FM, Cherry EM, Fenton FH, Koivumäki JT, Seemann G, Thul R, Zhang H, Sachse FB, Beard D, et al. Prog Biophys Mol Biol., 2011, 104(1-3): 2-21.
[52] Maas AH, Rozendaal YJ, van Pul C, Hilbers PA, Cottaar WJ, Haak HR, van Riel NA. A physiology-based model describing heterogeneity in glucose metabolism: the core of the Eindhoven Diabetes Education Simulator (E-DES). J Diabetes Sci Technol., 2015, 9(2): 282-292.
[53] Shiang KD, Kandeel F. A computational model of the human glucose-insulin regulatory system. J Biomed Res., 2010, 24(5): 347-364. DOI:10.1016/S1674-8301(10)60048-6
[54] De Gaetano A, Gaz C, Panunzi S. Consistency of compact and extended models of glucose-insulin homeostasis: The role of variable pancreatic reserve. PLoS ONE, 2019. https://doi.org/10.1371/journal.pone.0211331
[55] González AA, Voos H, Darouach M. Glucose-Insulin System Based on Minimal Model: A Realistic Approach. 2015 17th UKSim-AMSS International Conference on Modelling and Simulation (UKSim), Cambridge, 2015, 55-60. DOI: 10.1109/UKSim.2015.65
[56] Grygoryan R.D. High sustained G-tolerance model development.STCU#P-078 EOARD# 01-8001 Agreement: Final Report, 2002.
[57] Grygoryan RD, Hargens AR. A virtual multicellular organism with homeostatic and adaptive properties. In: Adaptation Biology and Medicine: Health Potentials. Ed. L. Lukyanova, N.Takeda, P.K. Singal. New Delhi: Narosa Publishing House, 2008, 5: 261-282.
[58] White RJ, Leonard JI, Rummel JA, Leach CS. A systems approach to the physiology of weightlessness. Journal of medical systems, 1982, 6(4): 343-358.
[59] Hensley DW1, Mark AE, Abella JR, Netscher GM, Wissler EH, Diller KR. 50 years of computer simulation of the human thermoregulatory system. J Biomech Eng., 2013, 135(2): 021006. DOI: 10.1115/1.4023383
[60] Alzeer AH, Wissler EH. Theoretical analysis of evaporative cooling of classic heat stroke patients. Int J Biometeorol. 2018, 62(9): 1567-1574. DOI: 10.1007/s00484-018-1551-1
[61] Wagar LE, DiFazio RM. Davis MM. Advanced model systems and tools for basic and translational human immunology. Genome Med. 2018, 10(73). https://doi.org/10.1186/s13073-018-0584-8.
[62] Kerepesi C, Bakács T, Szabado, T. MiStImm: an agent-based simulation tool to study the self-nonself discrimination of the adaptive immune response. Theor Biol Med Model, 2019, 16(9). https://doi.org/10.1186/s12976-019-0105-5
[63] Amosov NM, Paleys BL, Agapov BT, Yermakova II, Lyabakh KG, Solovev AA. Theoretical Investigations of Human Physiology. Kiev, Naukova Duma, 1977.
[64] Shim EB, Leem CH, Abe Y, Noma A. A new multiscale simulation model of the circulation: from cells to system. Philos Trans A Math Phys Eng Sci. 2006, 364(1843): 1483-1500. https://doi.org/10.1098/rsta.2006.1782
[65] Grygoryan RD. The Energy basis of reversible adaptation. N.Y.: Nova Science, 2012: 254. ISBN: 978-1-62081-093-4
[66] Grygoryan RD. The optimal circulation: cells contribution to arterial pressure. N.Y.: Nova Science, 2017: 287. ISBN: 978-1-53612-295-4
[67] Trayanova NA, Winslow R. Whole-Heart Modeling. Applications to Cardiac Electrophysiology and Electromechanics. Circulation Research. 2011, 108: 113-128. https://doi.org/10.1161/CIRCRESAHA.110.223610
[68] Noble D, Rudy Y. Models of cardiac ventricular action potentials: iterative interaction between experiment and simulation. Philos Trans R Soc Lond A. 2001, 359: 1127-1142.

DOI: https://doi.org/10.30564/jhp.v2i1.1905

[69] Rice JJ, Wang F, Bers DM, de Tombe PP. Approximate model of cooperative activation and crossbridge cycling in cardiac muscle using ordinary differential equations. Biophys J., 2008, 95: 2368-2390.

[70] Niederer SA, Hunter PJ, Smith NP. A quantitative analysis of cardiac myocyte relaxation: a simulation study. Biophys J. 2006, 90: 1697-1722.

[71] Trayanova NA, Winslow R. Whole-Heart Modeling: Applications to Cardiac Electrophysiology and Electromechanics. Circulation Research. 2011, 108: 113-128.
https://doi.org/10.1161/CIRCRESAHA.110.223610

[72] Kerckhoffs RC, Neal ML, Gu Q, Bassingthwaighte JB, Omens JH, McCulloch AD. Coupling of a 3D finite element model of cardiac ventricular mechanics to lumped systems models of the systemic and pulmonic circulation. Ann Biomed Eng., 2007, 35: 1-18.
DOI: 10.1007/s10439-006-9212-7

[73] Walpole J, Papin JA, Peirce SM. Multiscale computational models of complex biological systems. Annu Rev Biomed Eng. 2013, 15: 137-154.
DOI: 10.1146/annurev-bioeng-071811-150104

[74] Jie X, Gurev V, Trayanova N. Mechanisms of mechanically induced spontaneous arrhythmias in acute regional ischemia. Circ Res. 2010, 106: 185-192.
https://doi.org/10.1161/CIRCRESAHA.109.210864

[75] A. Hosoi, T. Washio, J. Okada, Y. Kadooka, K. Nakajima, T. Hisada. A Multi-Scale Heart Simulation on Massively Parallel Computers. SC'10: Proceedings of the 2010 ACM/IEEE International Conference for High Performance Computing, Networking, Storage and Analysis, New Orleans, LA, 2010, 1-11.
DOI: 10.1109/SC.2010.5

[76] Grygoryan R.D., Aksenova T.V., Degoda A.G. A simulator of mechanisms providing energy balance in human cells. Cybernetics and Computing Technologies. 2017, 2: 67-76.
DOI: https://doi.org/10.15407/kvt188.02.065

 DOI: https://doi.org/10.30564/jhp.v2i1.1905