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SIMULATING OF HUMAN PHYSIOLOGICAL SUPERSYSTEMS: MODELING OF KIDNEY AND BLADDER FUNCTIONS

A quantitative model describing the functions of human kidney and bladder is created. The model is realized and tested as an autonomous C# software module (SM) functioning under given dynamic input characteristics. Finally, SM will be incorporated into our specialized general software capable of simulating the main modes of human integrative physiology, namely, interactions of physiological super-system (PSS). The model of the kidney describes mechanisms of blood filtration in Bowman's capsule, reabsorption in collecting tubules, as well as the central renin-angiotensin system mechanism. The model of the bladder describes the dynamics of its filling and periodic emptying. Each act of bladder emptying is initiated by a signal generated by the brain in response to afferent impulse patterns from the bladder's mechanoreceptors. Models have been tested using algorithms that design scenarios, including simulation of either short-time or long-time (hours or days) observations. Input data include different combinations of pressure in renal afferent arterioles, osmotic, and oncotic blood pressures. Output data includes dynamics of primary urine, final urine, bladder volume, urine pressure, mechanoreceptors' activity, renin production velocity, blood renin concentration, angiotensin2 production velocity, and blood angiotensin2 concentration, as well as blood albumin and sodium concentrations. Both student-medics and physiologists interested in providing theoretical research can be users of SM.
Keywords: physical health, kidney, bladder, physiological mechanisms, quantitative model, simulator.

Introduction

Human organs and certain anatomical-functional systems (AFS) form very complex functional systems known as physiological super-systems (PSS). The general concept of human PSS [1-3] explained deep cellular mechanisms that determine cells interaction for providing of every AFS's actually optimal parameters. However, traditional empiric physiology possesses not by research technologies capable of establishing the main quantitative laws ruling the functionalities of PSS. Potentially, mathematical models could help in solving this problem. But traditional methodology of modeling is focused on creating models of individual organs functioning under known input disturbances. Such models are not suitable for the theoretical study of integrative physiology. To fill this methodological gap in, we need models that take into account both cell-scale autonomous mechanisms and multi-scale multicellular regulatory mechanisms. Moreover, the methodology itself must contain a new and explicit understanding of the rules for the coexistence of populations (colonies) of specialized cells. Namely, such approach to the modeling and computer simulating of human physiology is proposed in [4-8]. Their main novelty is in combining of multi-level physiological mechanisms for explaining of organism-scale adaptive physiological responses to environmental alterations. In fact, this approach also creates potentials for explaining mechanisms that determine the dynamic multi-parametric shape of human physical health (HPH). Such a theoretical fundament is extreme necessary for the individualization of the medical assessment of HPH.

Special model of the thermoregulatory system (MT) recently was presented in [8]. The main reason for its creation was that MT should be compatible with our other models. For solving our problems in the frame of human PSS, it is sufficient to have an MT containing three body compartments: a core (it represents muscle, subcutaneous tissue, and bone), skin, and blood.

Working versions of autonomous C# software modules (SM) help us during the tuning of main model constants and testing

special regimes of the model functioning autonomously. Such simulations imitate traditional physiological investigations in which the input-output relationships of the isolated organ have been established using animal-based experiments.

The goal of this article is to present our latest development – a complex model describing main functions of kidneys and a bladder.

Mathematical model of kidneys

Different models of kidney function have been proposed to clarify the mechanism and peculiarities of human kidneys functioning under physiological conditions and in certain diseases. Perhaps, within the framework of this article, it is sufficient to cite the following publications [9-15].

1. Physiological background

Kidneys represent a specific organ which has its complex structure and provides multiple functions. Nephrons are structural-functional units of every kidney. A nephron in turn is composed of a Bowman's capsule which surrounds the glomerular capillary loops and participates in the filtration of blood from the glomerular capillaries. Bowman's capsule also creates a urinary space through which filtrate (primary urine) can enter the nephron and pass to the proximal convoluted tubule. The latter provides reabsorption of about 99% of water and solved chemicals like glucose, sodium, potassium, magnesium, chlorine ions. Through convoluted tubule the final concentrated urine enters and accumulates in the bladder, from where it is evacuated as it becomes critically full. So, the main kidney function is in controlling of blood chemical composition and total blood volume. As the latter is one of the main determiners of long-term mean arterial pressure, kidneys play essential role in both circulation and blood chemical composition. The latter is essential for providing due velocities of cell metabolism.

The model of CVS is presented in [6,7], thus we omit its description in detail. Perhaps, it is sufficient to note that our CVS-model currently is the most complex model, including mechanisms of circulation's both acute and long-term control.

The most distinguishing sign of every PSS is that it functionally integrates multiple AFS. The extreme necessity in novel models is conditioned with the practical impossibility to provide quantitative empirical research of complex and multi-level mechanisms governing the interaction of multiple HPSS in physiological or pathological conditions. At the same time, it is clear that often complex pathologies appear because of inadequate functioning one or more functional chains of PSS. So, an alternative – simulative research of human PSS is highly encouraged.

In parallel with the crating of novel models, several models created in the frame of the traditional methodology can be re-vised in the light of the PSS concept. Our current publication, presenting such an approach, illustrates both the modeling technology and the main problems arising under its application to models published earlier [6,7]. These publications were chosen because AFSs of this PSS represent organs and systems that are external providers of cellular metabolism. As to its intracellular optimizers, briefly described in [1] (only the energy aspect), we intend to create a special model that has to include also those nuclear mechanisms that are under cytoplasm-released adaptation factors. Namely, these factors increase/decrease the expression of genes in specific sites of DNA.

Special software does provide both tunings of models and all procedures accompanying a wide range of their simulation research. Such work is too big to be made within a usual short-term research project and described in a usual research article. Therefore, we are publishing each interim developmental result that can also be an autonomous unit-software. The final purpose of this multi-stage developmental project is to provide physiologists-researchers with modern computer-based information technology with dual goals. The first goal is simulation research of human certain complex PSSs. The second goal is to provide professors and medical students with a modern specialized visualization technology capable of helping future medics to better understand the physiological basis of non-trivial pathologies.

2. *A model of blood filtration in glomeruli of a nephron*

Schematically, the functional model of kidneys is shown in fig.1.

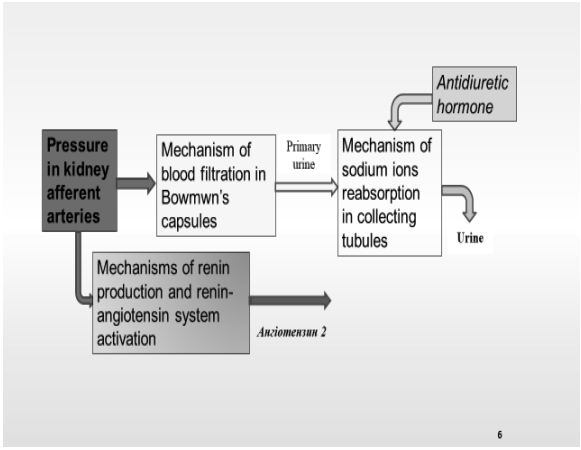

Fig.1. Functional model of kidneys

The equation for the blood filtration dynamics in the glomeruli of the nephron causally relates the velocity of filtration rate $v_k(t)$ to the total (hydrostatic, oncotic, and osmotic) pressure $P_\Sigma(t)$ in Bowman's capsule as:

$$\frac{dv_k(t)}{dt} = \begin{cases} \eta_k \cdot P_\Sigma(t) - v_k(t) & , P_\Sigma(t) > P_{pu}(t) \\ 0 & , P_\Sigma(t) \le P_{pu}(t) \end{cases},$$

$$P_\Sigma(t) = P_h(t) - P_{os}(t) + P_{on}(t),$$

where η_k - is an approximation constant.

A model of sodium reabsorption in the collecting tubules of the nephron is described by a system of differential equations that take into account urine volume (V_u) and sodium concentrations in corresponding sections of tubules ($C_{Na}, C_{Na}^{pc}, C_{Na}^{ct}$):

$$\frac{dNa_{pc}}{dt} = \eta_1 \cdot C_{Na} + Na_{ab,} - Na_{reabpc,} - q_{pc} \cdot C_{Na}^{pc},$$

$$\frac{dV_u}{dt} = q_{ct},$$

$$\frac{dNa_u}{dt} = q_{ct} \cdot C_{Na}^{ct},$$

Hormonal control of the reabsorption dynamics, based on concentrations of albumin (Al) and antidiuretic hormone (Adh), is described by the following system of equations:

$$Na_{reabdc} = S(Al) \cdot Na^*_{reabdc}$$

$$\frac{dAl}{dt} = K_{Al} \cdot \Delta C_{Na}^{KA} - D_{Al} \cdot Al,$$

$$q_{reab}^{ct} = S(Adh) \cdot q_{reab}^{ct*},$$

$$\frac{dAdh}{dt} = K_{Adh} \cdot \Delta C_{Na}^{u} - D_{Adh} \cdot Adh,$$

$$W_{reab} = W^{ct}{}_{reab} + W^{pc}{}_{reab},$$

$$Na_{reabpc} = W^{pc}{}_{reab} \cdot C_{Na}^{pc}.$$

The normalized response of the reabsorption rate to the hormone concentration is described by the function $S(x) = \frac{a \cdot x^n}{b + x^n}$.

3. *A model of the central renin-angiotensin system*

Despite the natural activation of the central renin-angiotensin system (CRAS) mechanism plays only a secondary role in the main function of the kidneys, the fact that the receptor link of CRAS is located precisely in the afferent arterioles of the kidneys deserves our special attention to CRAS. It is one of the powerful hormonal mechanisms of long-term regulation of mean arterial pressure (MAP).

The physiology of CRAS begins with the secretion of renin ($R(t)$) in the kidneys and ends with the formation of the vasoactive agent angitonensin2 ($A^{II}(t)$) in the liver. When modeling, we omit some intermediate transformations. Using the following system of equations, we describe the relationship between the perfusion pressure $P_{aa} - P^T{}_{aa}$ in the kidney afferent arteries and $R(t)$:

$$\frac{dR}{dt} = \begin{cases} \lambda_R \cdot (P_{aa} - P^T{}_{aa}) - R_{ut}, & P_{aa} > P^T{}_{aa} \\ -R_{ut}, & P_{aa} \le P^T{}_{aa} \end{cases}$$

In the second differential equation, which includes the amount of $A^{II}(t)$ in the blood concentration of renin, A_{utI}^{II} is the rate of angitonensin2 molecules of disintegration.

$$\frac{dA^{II}}{dt} = \begin{cases} \delta_{RA} \cdot (R - R^T) - A_{utI}^{II}, & R(t) > R^T \\ -A_{utI}^{II}, & R(t) \le R^T \end{cases}.$$

In these equations, parameters λ_R, $P^T{}_{aa}$, R_{ut}, δ_{RA}, and R^T are approximation constants.

The last three equations take into account the effects of angitonensin2 on vascular parameters in the CVS model:

$$U_i(t) = U_i(0) - \vartheta_i \cdot A^{II},$$

$$D_i(t) = D_i(0) + \vartheta_i \cdot A^{II},$$

$$r_i(t) = Z(V_i(t), D_i(t), U_i(t)),$$

where ϑ_i are approximation constants for each vascular compartment.

4. *A model of bladder's filling-emptying*

A special model for simulations of the periodic dynamics of bladder's filling and emptying is created. In this model, the volume of urine, that gradually accumulates in the bladder and creates pressure in it, is the input variable. This volume is also an input variable of bladder's mechanoreceptors, which have a sensitivity threshold and a saturation level. Therefore, when the afferent pulse rate is approaching to the saturation level, a signal born in the brain is sent in a downward direction to the bladder to create a muscular effort for urine expelling.

For the formal description of these physiological acts following additional variables are introduced: 1) t_b conditional time within the filling-emptying cycle; 2) V_b bladder volume; 3) P_b bladder pressure and volume; 4) D_b stiffness of the bladder; 5) r_b bladder outlet valve resistance; 6) q_b flow of urine; 7) R_{bm} activity of bladder mechanoreceptors; 8) ΔP_b additional pressure.

$$r_b(t_b) = \begin{cases} r_b^{\max}, & P_b(t_b) < P^{\max} \\ r_b^{\max} - (r_b^{\max} - r_b^{\min}) \cdot t_b, & V_b(t_b) \geq V_b^{\min} \end{cases},$$

$$\frac{dV_b}{dt} = q_{ct} - q_b,$$

$$R_{bm}(t) = \begin{cases} 0, & R_{bm}{}^T > P_b(t) \\ \dfrac{1 - e^{(\upsilon \cdot (R_{bm}{}^T - P_b(t))}}{1 + \psi \cdot e^{(\upsilon \cdot (R_{bm}{}^T - P_b(t))}}, & R_{bm}{}^T \leq P_b(t) \leq P_b^S \\ 1, & P_b(t) > P_b^S \end{cases},$$

$$P_b(t_b) = \begin{cases} 0, & V_b(t_b) < V0_b \\ (V_b(t_b) - V0_b) D_b(t_b), & V_b(t_b) \geq V0_b \end{cases},$$

$$q_b(t_b) = P_b(t_b) / r_b(t_b),$$

where $R_{bm}{}^T$, $r_b^{\max}$, $r_b^{\min}$, $P^{\max}$, $V_b^{\min}$, υ, P_b^S, $V0_b$, and ψ - are approximation constants.

Main simulation results

In the frame of this article, we consider test simulations of the autonomous kidney-bladder model. In intact organism, values of input variables are provided by the organs that are directly or indirectly interacting with kidneys.

A simulation of the autonomous kidney-bladder model requires previous setting of both model constants and values of those variables that normally have been provided by other organs. Special window created for providing the tunings for a simulation is shown in fig.2. Once set, the input values are still working for multiple simulations until the user is interested in simulating of effects caused by new input data combination. This article does not provide the reader by simulation data reflecting effects of concrete diseases. All simulations shown below have a goal to demonstrate the fact that our models and the software technology, despite being an interim product yet, are a promising scientific tool. After a proper modification, the proposed software can be used for mining of additional information concerning functions of kidneys and bladder.

Figures 3-6 illustrate dynamics of a group of physiological characteristics during 6-hours simulation in human rest condition in horizontal position.

As shown in fig.3, urine formation depends on differences between primary urine and water reabsorption.

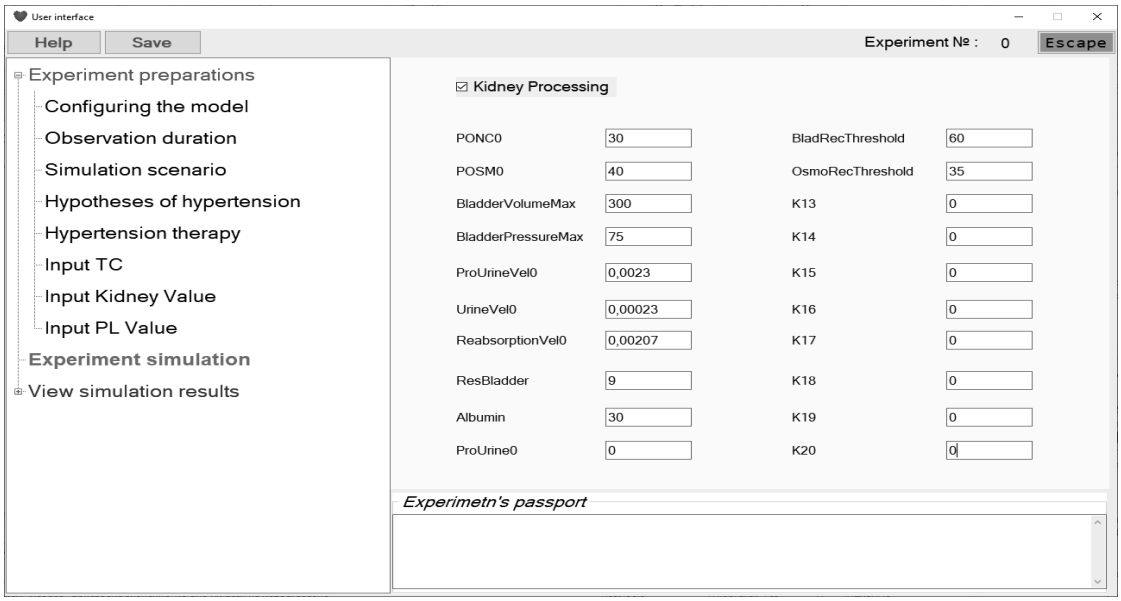

Fig.2. User interface fragment: special window for setting initial data necessary for processing the kidney model.

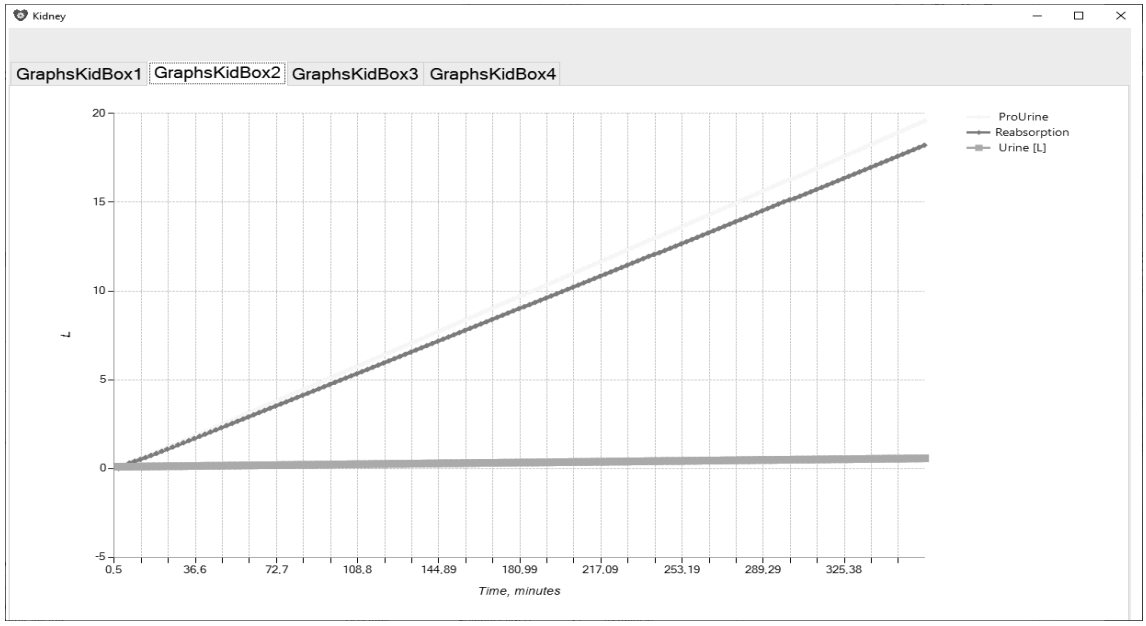

Fig.3. Dynamics of primary urine (Pro-urine) water reabsorption and final urine during six-hours observation (simulation data).

Fig.4. collects dynamics of bladder volume, bladder pressure, blood oncotic, and osmotic pressures. Bladder volume and pressure almost linearly increase with time until bladder mechanoreceptors (their dynamics see in fig. 5) reach a critical level for generating a brain efferent signal (additional pressure to bladder filling pressure) and opening of bladder's output sphincter. Just after this signal, bladder volume and pressure almost linearly decrease to their initial values. This is a simulation of a single cycle of bladder filling-emptying. According to simulation algorithms, such cycles can occur many times if the observation time is bigger than we simulated. Pay attention that in fig.5 the second variable (activity of osmotic receptors) is still at low and practically stable level. Certainly, in case of real and variable composition of blood salts, osmotic receptors will have appropriate activity and the reflex will play a proper role in arterial pressure, blood circulation, and in kidneys function. Fig.6 collects three variables: blood concentrations of albumin, sodium, as well as a conventional variable characterizing the energy status of kidneys. It is well known that the

sodium reabsorption in collecting tubules is an active ion transport against concentration gradients. This is a work provided by use of ATP molecules. Kidneys, despite their relatively little mas, are very "expensive" organ requiring about 20% of ATP synthesized in organism. Namely, this circumstance does play an essential role in efficiency of organ's function under general deficiency of energy sources like carbohydrates and oxygen. These aspects of organism-scale functioning cannot be theoretically analyzed otherwise than using proper models that describe functions of organs depending on their current energy status.

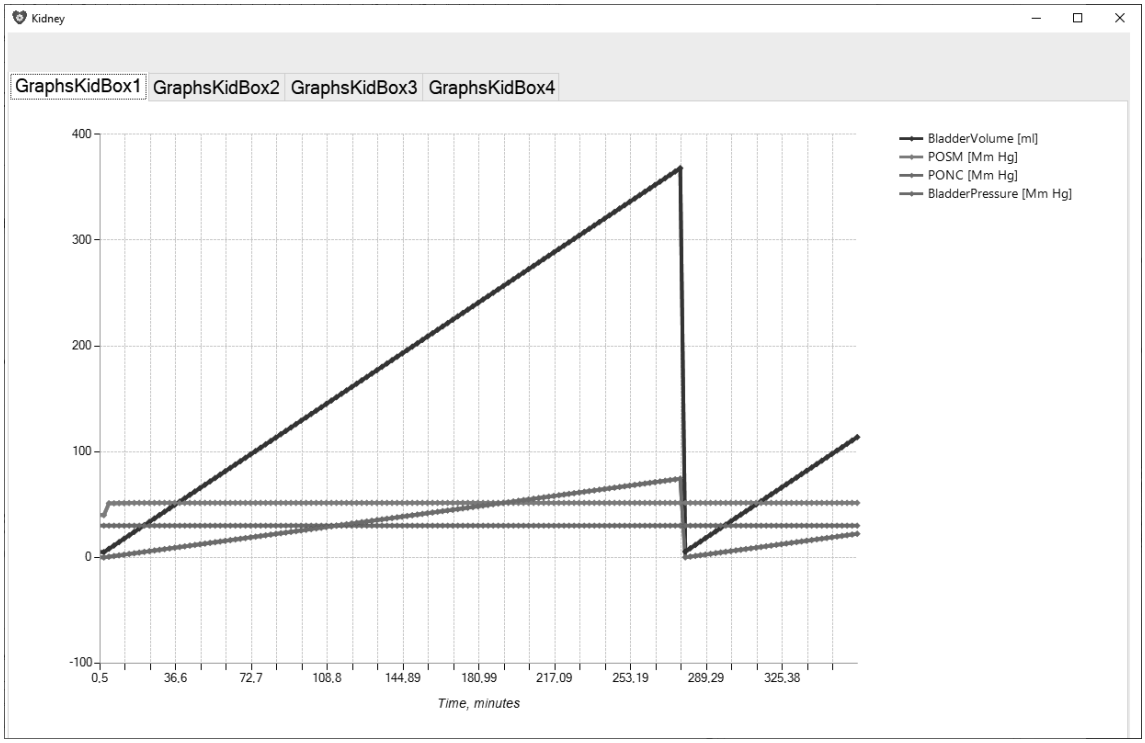

Fig.4. Dynamics of bladder volume and pressure, blood osmotic and oncotic pressures during six-hours observation (simulation data).

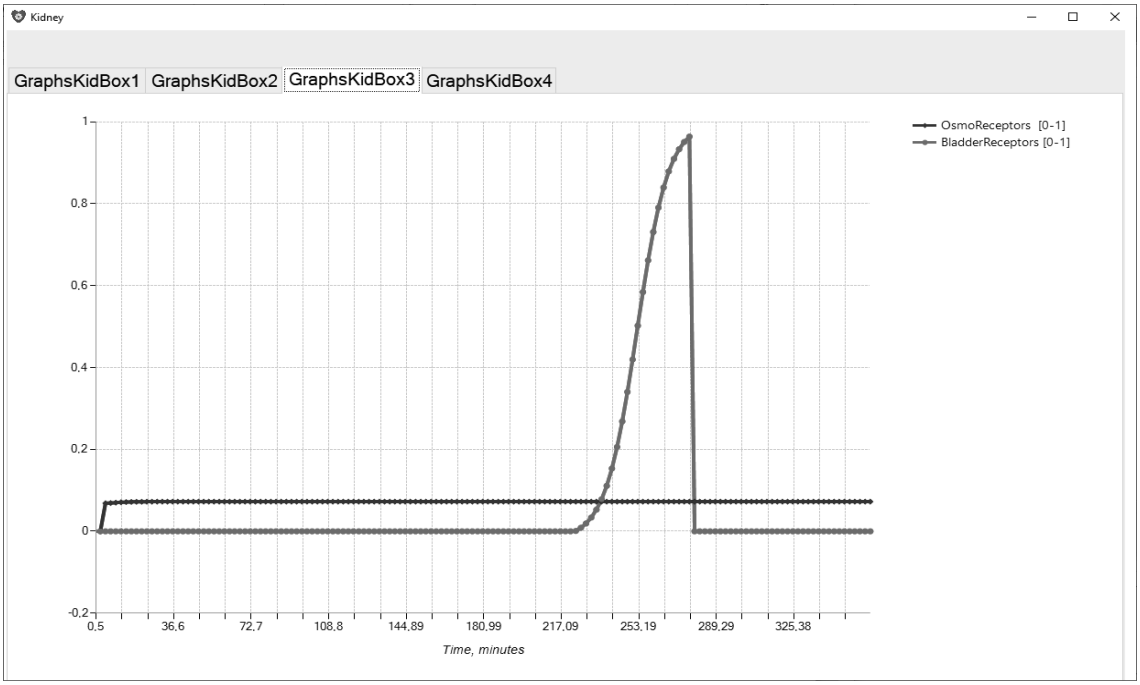

Fig.5. Dynamics of brain osmoreceptors and bladder mechanoreceptors during six-hours observation (simulation data).

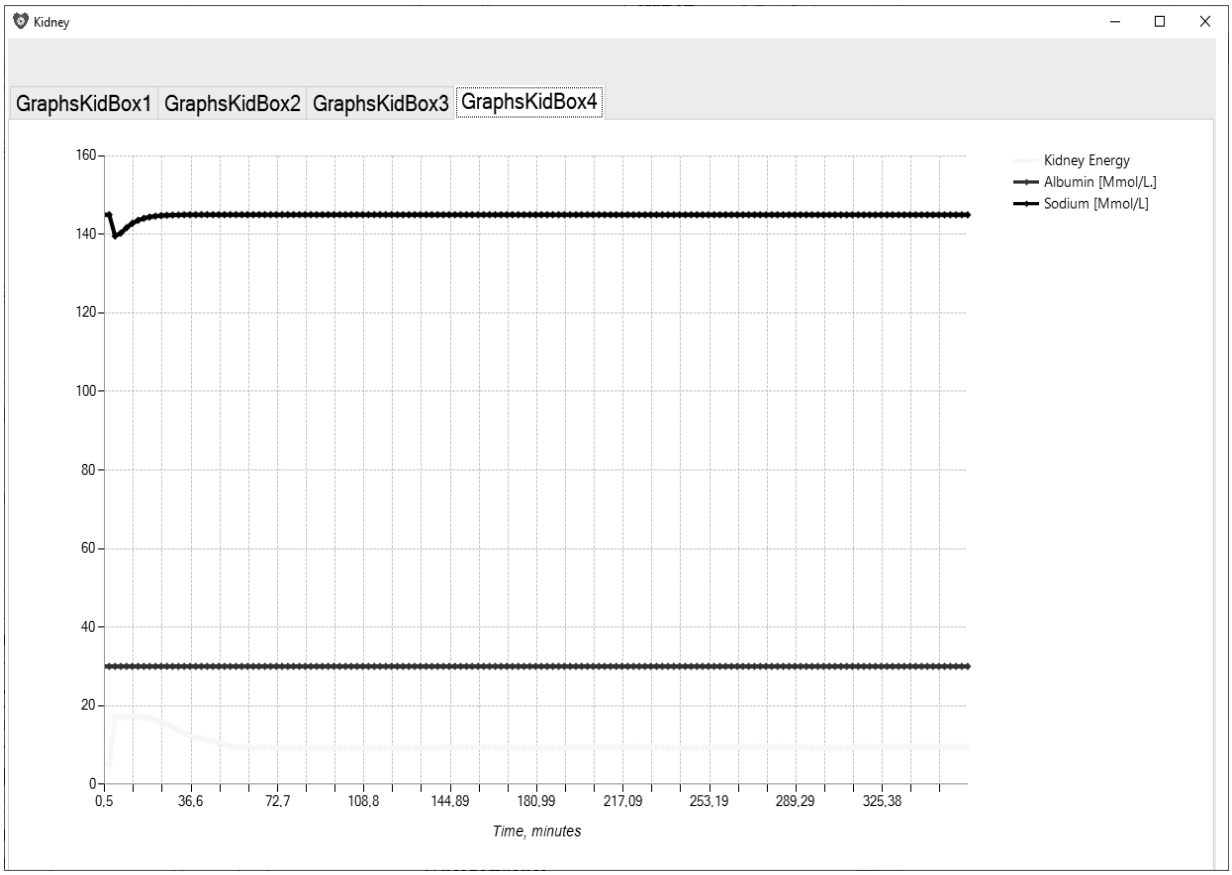

Fig.6. Dynamics of blood albumin, and sodium concentrations, as well as kidneys energy status six-hours observation (simulation data).

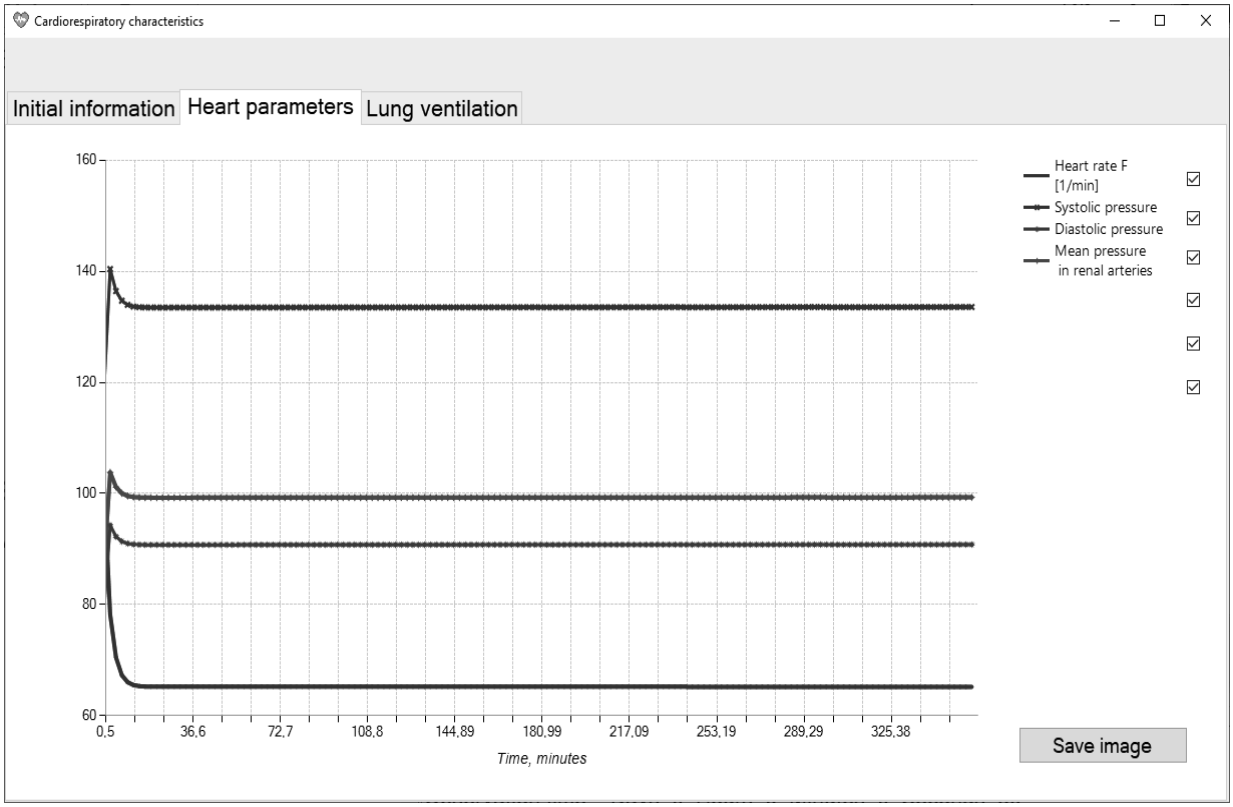

Fig.7. Dynamics of several hemodynamic variables (heart rate, systolic and diastolic pressures, mean pressure in renal arteries) during six-hours observation (simulation data).

Certainly, our simulator yields much more output data concerning not only kidney-bladder functions but also relating to blood circulation parameters, activities of baroreceptors, chemoreceptors, and dynamics of main endocrine hormones. Most hormones modulate not only the state of CVS but also the state of those body structures that concern the functionality of kidneys. An example of additional simulation data contains the fig. 7. It presents dynamics of several hemodynamic variables (heart rate, systolic and diastolic pressures, and the mean pressure in renal arteries) during six-hour observation. We do not present more such additional data for two main reasons. The first one is already mentioned above – the limited paper volume. The second reason is concerned with the "raw" state of the model. Values of several constants and variables are included in the model in conventional units only. We plan to advance the final model when all component models will be created and integrated into the complex simulator of human PSS.

Conclusions

In order to extend the potentials of the PC-based simulator of the human physiological super-system (PSS), a special quantitative model of the human kidneys and a bladder is created and mainly tested. The kidneys model describes: 1) the mechanism of blood filtration in Bowman's capsule and dynamics of primary urine formation; 2) the mechanism of water and sodium reabsorption in conducting tubules; 3) the mechanism of bladder dynamic filling and periodic emptying using afferent patterns of bladder's mechanoreceptors; 4) the central renin-angiotensin-aldosterone (CRAS) mechanism which is one of main determiners of long-term MAP. Algorithms provide designing of scenarios including simulation of either short-time or long-time (hours or days) observations. Test simulations presented in the article covering six-hours observation of kidney-bladder function. Adequateness of models gives us an opportunity to incorporate them into special software-modeling research tool with a final goal to provide theoretical investigations of human PSS.

In a near future, this simulator is to be widened by two more models: 1) of mechanisms controlling lung ventilation; 2) of mechanisms controlling liver-pancreas interaction. These additional mechanisms specifically modulate circulation and cells metabolism.

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