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SIMULATING OF HUMAN PHYSIOLOGICAL SUPERSYSTEMS: INTEGRATIVE FUNCTION OF ORGANS SUPPORTING CELL LIFE

A quantitative model of fluids’ dynamics (MFD) in the human body is created. Initially, MFD was realized as an autonomous C# software module (SM) functioning under given dynamic input characteristics. Later, SM was incorporated into our special software-modeling tool (SMT) capable of simulating the main modes of the human physiological super-system (PSS) providing cells' life. MFD describes mechanisms regulating long-term blood, lymph, total cells’, and intercellular volumes. SMT simulates both intracellular and multicellular mechanisms providing cell energy balance despite casual dynamics of energy consumption rate. Multicellular mechanisms include complex systems controlling systemic and regional hemodynamics, interaction of the liver with the pancreas, blood filtration in kidneys, bladder function, and liquid expirations in lungs and skin in the background of a dynamic external environment. The latter is a gas atmosphere with altering pressure, illumination, temperature, humidity, and wind speed. 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 internal and external parameters including osmotic, and oncotic pressures. Output data include the main parameters characterizing organs and life support systems. Both student-medics and physiologists interested in providing theoretical research can be users of SM.
Keywords: physical health, body fluids, physiological control, quantitative model, simulator

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СИМУЛЯТОР ФІЗІОЛОГІЧНИХ НАДСИСТЕМ ЛЮДИНИ: ІНТЕГРАТИВНА ФУНКЦІЯ ОРГАНІВ ЖИТТЄЗАБЕЗПЕЧЕННЯ КЛІТИНИ

Створено кількісну модель динаміки рідин (РРР) в організмі людини. Спочатку MFD був реалізований як автономний програмний модуль C# (SM), що функціонує при заданих динамічних вхідних характеристиках. Пізніше SM було включено в наш спеціальний інструмент програмного моделювання (SMT), здатний моделювати основні режими фізіологічної суперсистеми людини (PSS), що забезпечує життєдіяльність клітин. MFD описує механізми довготривалої регуляції крові, лімфи та загального внутрішньоклітинного та міжклітинного об’ємів. SMT моделює як внутрішньоклітинні, так і багатоклітинні механізми, що забезпечують енергетичний баланс клітини, незважаючи на випадкову динаміку швидкості споживання енергії. Багатоклітинні механізми включають складні системи контролю системної та регіональної гемодинаміки, взаємодії печінки з підшлунковою залозою, фільтрації крові в нирках, функції сечового міхура, виділення рідини в легенях і шкірі на тлі динамічного зовнішнього середовища. Останнє являє собою газову атмосферу зі змінним тиском, освітленістю, температурою, вологістю та швидкістю вітру. Моделі були перевірені з використанням алгоритмів, які розробляють сценарії, включаючи симуляцію короткочасних або тривалих (години або дні) спостережень. Вхідні дані включають різні комбінації внутрішніх і зовнішніх параметрів, включаючи осмотичний і онкотичний тиск. Вихідні дані містять основні параметри, що характеризують органи та системи життєзабезпечення. Користувачами СМ можуть бути як студенти-медики, так і фізіологи, зацікавлені у проведенні теоретичних досліджень.
Ключові слова: фізичне здоров’я, рідини організму, фізіологічний контроль, кількісна модель, тренажер

Introduction

Physiologists and physicians use empirical technologies to measure a limited number of life parameters that can quantitatively characterize the level of human physical health (HPH). Certainly, these parameters were statistically verified for populations of healthy and seek people. However, physicians meet a problem: the parametric landscape of HPH displays essential and often very complex alterations in time [1-3]. The origin of the observed instability of life parameters is still unknown. Moreover, neither physiologists nor medical scientists have ideas for conceptual overcoming the problem. In our opinion, the concept of physiological supersystems (PSS) [4-6], properly realized as a specialized computer simulator, could essentially assist in finding a way out of this methodological dead-end. The simulator must be based on special quantitative models of organs and anatomical-physiological systems that, according to PSS, were saved in vertebrates due to the essential role of these organs in evolution. Basic mathematical models and software components have been already developed [7-10].

The article proposes our vision of the final model, which integrates these components. Additionally, the article presents several test simulations demonstrating the potential of our software for physiologists and physicians.

Mathematical model of PSS

According to the concept of PSS, optimal cell metabolism is a fundamental condition for the cellular long life and functionality in unstable external/internal environments. Interactions between certain biochemical factors (also known as adaptation factors [1,11,12]) of every specialized cell and its nucleus adapt the expression of genes responsible for the efficiency of many molecular events including the rate of energy (ATP molecules) synthesis. However, the efficiency of autonomous intracellular regulators essentially falls in parallel with an increasing imbalance between biosynthesis and molecular destruction. Therefore, special adaptation factors, produced in these problematic cells and penetrated lymph or intercellular space, finally modify the activity of multiple multi-cellular mechanisms (MM). Some of MM enhances the basic intracellular regulators. In particular, a set of MM provides molecular rebuilding in the problematic cells with materials (oxygen, water, nutrients). Another group of MM purifies the cytoplasm in these cells. So, the entire organism is chronically under the influence of adaptation factors. This is the humoral mechanism capable of originating HPH's instability. As many chemicals influence target neurons of CNS, the latter also modifies the parametric landscape of HPH. It is the understanding that the landscape depends on the number of problematic cells.

Every cell is a dynamic object adaptively compensating for intracellular destructions. In this context, one of the roles of MM is providing intracellular adaptive re-buildings with adequate inflows of primary materials (nutrients, oxygen, and water). The second role of MM provided by other organs is in adequately removing metabolic wastes. To provide such a requirement, PSS must have a rather complex construction. It was shown [5,6] that the digestive system, lungs, cardiovascular system (CVS), liver, pancreas, kidneys, thermoregulatory system (TS), as well as special neural-hormonal mechanisms providing the fluids' homeostasis are components of the PSS to be modeled. The main structural-functional blocks of PSS and their interrelations are illustrated in Fig. 1.

According to Fig.1, body fluids are partially located in four main reservoirs: cellular, intercellular, cardiovascular, and lymphatic. The cardiovascular system (CVS) is the primary space for receiving the fluids absorbed in the gastrointestinal tract. A part of blood through capillaries penetrating the interstitial liquid space is the internal source for cells taking oxygen and nutrients. The blood, remaining in capillaries, flows into venous capillaries and veins finally filling the central vein which is the reservoir for filling the right heart. So, in statics, the blood volume that leaves CVS and lymphatic return to CVS are equal. However, multiple factors can violate this equality.

The interstitial reservoir plays a dual role. It is the second source of lymph and the space for the liquid exchanging with cells. The

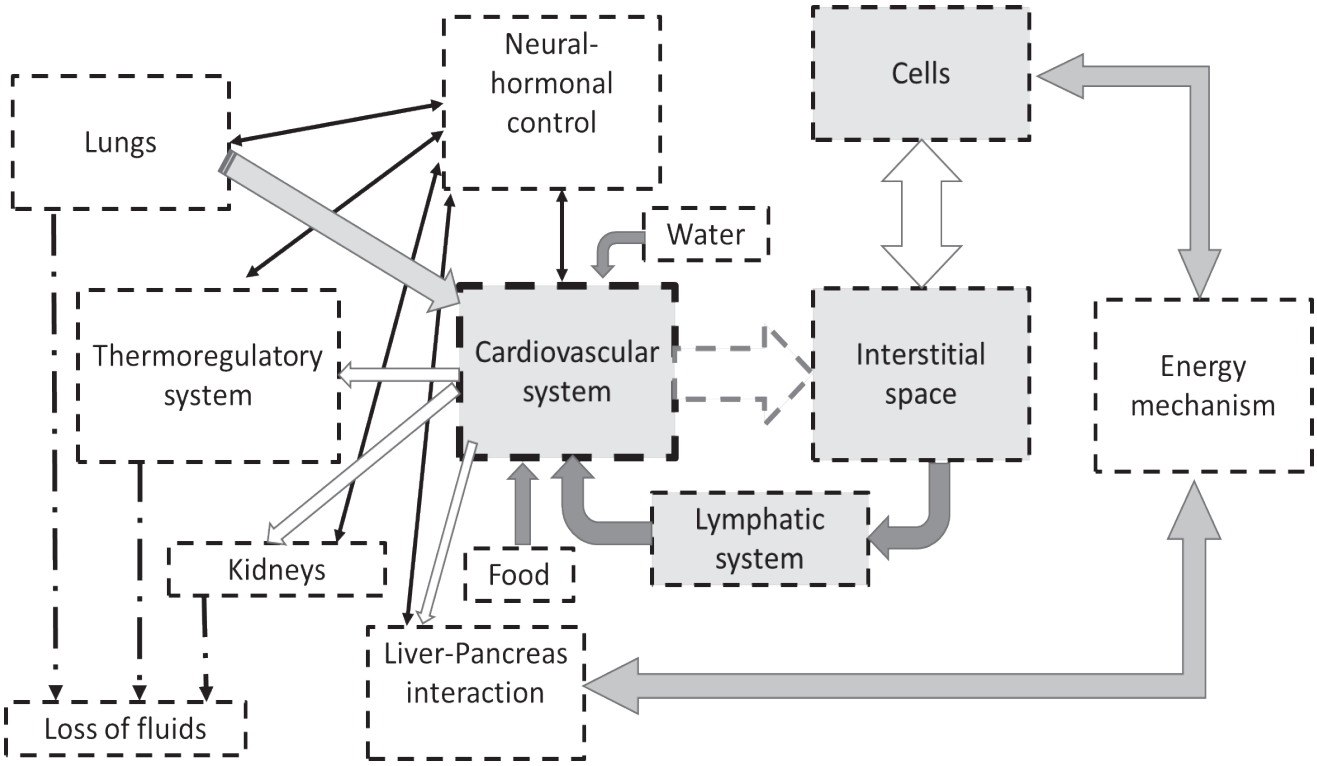

Fig. 1. Interaction of organs and anatomical-functional systems involved in PSS

cellular liquid contains both oxygen and nutrients. They are internal sources for the molecular synthesis of specific biological macromolecules. A part of them (molecules of ATP) provides all forms of intracellular biological work. Other macromolecules are ultra-structural units for constructing cellular organelles.

Thanks to liver-pancreas interaction, excess blood sugars can be transformed and accumulated into the liver as glycogen. Under low blood concentrations of glucose, this glycogen is back-transformed to glucose.

The dynamics of boy fluids are associated with the activities of multiple specialized organs that are under the influences of nervous and hormonal regulators. Models of these mechanisms have been already published by us [7-10].

Fluids can leave the body in three main ways – blood filtration in the kidneys, skin sweating (this is under mechanisms controlling the thermoregulation), and lung expiration. Therefore, the total body fluids and their parts in the four relatively isolated internal spaces can display complex dynamics depending on multiple external and internal factors. Our models were properly advanced: the dynamics of internal fluids' redistributions are described.

Let us denote the body's total fluid volume for every time moment as $V_T(t)$. It can be presented as a sum of four components:

$$V_T(t) = V_{CVS}(t) + V_{VC}(t) + V_{In}(t) + V_{Ly}(t) \quad (1)$$

In (1), V_{CVS} is the total blood volume, V_{VC} is the total liquid into cells, V_{In} is the volume of the intercellular space, and V_{Ly} is the lymphatic volume.

$V_{CVS}(t)$ depends on the velocity of blood's inflows and outflows. Let us the water inflow is $q_{Inp}(t)$, $q_{LE}(t)$ is the outflow (expiration) in lungs, $q_{SE}(t)$ is the evaporation through the skin, $q_U(t)$ is the urine outflow, $q_{VCI}(t)$ and $q_{VCC}(t)$ are the flows of liquid into and out of a virtual cell, $q_{In}(t)$ is the inflow into the intercellular space, $q_{Cf}(t)$ is the filtration in capillaries, and $q_{Ly}(t)$ is the lymph flow. Then, the differential equations (2)-(5) below describe relationships between volumes and liquid flows:

$$\frac{dV_{CVS}}{dt} = q_{Inp}(t) - q_{LE}(t) - q_{SE}(t) - q_U(t) - q_{Cf}(t) - q_{In}(t) + q_{Ly}(t) \quad (2)$$

$$\frac{dV_{VIn}}{dt} = q_{Cf}(t) - q_{VCC}(t) - q_{Ly}(t) \quad (3)$$

$$\frac{dV_{VCC}}{dt} = q_{Cf}(t) - q_{Ly}(t) \quad (4)$$

$$\frac{dV_{VLy}}{dt} = q_{VCC}(t) - q_{Ly}(t) \quad (5)$$

The next system of equations (6)-(8) describes relationships between flows, pressures, and resistances in compartments:

$$q_{Cf}(t) = (P_C(t) - P_{In}(t)) / R_C(t) \quad (6)$$

$$q_{In}(t) = (P_{In}(t) - P_C(t)) / R_{InC}(t) \quad (7)$$

$$q_{Ly}(t) = (P_{Ly}(t) - P_{CV}(t)) / R_{Ly}(t) \quad (8)$$

In (6)-(8), $P_C(t)$ is capillaries' pressure, $R_C(t)$ is capillaries' resistance, $P_{In}(t)$ is interstitial liquid's pressure, $R_{InC}(t)$ is the resistance between interstitial and cell spaces, $P_{Ly}(t)$ is the lymphatic pressure, P_{CV} is the central vein pressure, and $R_{Ly}(t)$ is the resistance of lymphatic collector.

So, the equations' system (1)-(8) is incorporated into our algorithms developed for computer simulations of complex physiological mechanisms responsible for physical health. Calculations of pressures include the hydrostatic and osmotic (oncotic) components. Namely, two latter components play a key role in mechanisms that control the acid-basis and electrolytic homeostasis.

Brief information about research software

Simulation algorithms are similar to those published in [8,9]. Every simulation starts from the actualization of input data and simulation scenarios. These procedures are provided with assistant window forms. The simulation scenario covers both the simulation duration and combinations of dynamic tests. Our early software versions provided the user with simulation graph results only after the entire scenario was processed. The calculation algorithm was modified to make simulations more effective without using a more empowered computer. To construct graphs, the modified algorithm creates and saves a series of data only for three neighbor time points (previous, current, next). This cardinally increased the real-time observation to be simulated. It can be both several seconds and several weeks. However, under long-lasting simulations, the user was not informed about the simulation dynamics which sometimes can be wrong. Thus the algorithm is modified to illustrate the calculation dynamics for a representative group of biometric characteristics that can inform the modeler whether the simulation goes in the planned course.

Main simulation results

The limited space of the article forced us to consider a limited number of test simulations. At the same time, we tried to illustrate both the simulation technology that may be interesting for programmers and several biological data that could attract physiologists and medics-researchers who are interested in widening the research methods.

This article does not provide the reader with simulation data reflecting the effects of concrete diseases. All simulations shown below have to demonstrate that our models and the software technology, despite being an interim product yet, are promising scientific tools. Perhaps, physiologists and medics-researchers as potential users of our software will know that after a proper modification, the proposed software can be used for mining additional information concerning functions of every organ involved in PSS.

Figures 2 and 3 illustrate special graph forms, providing tuning procedures for appropriate model components.

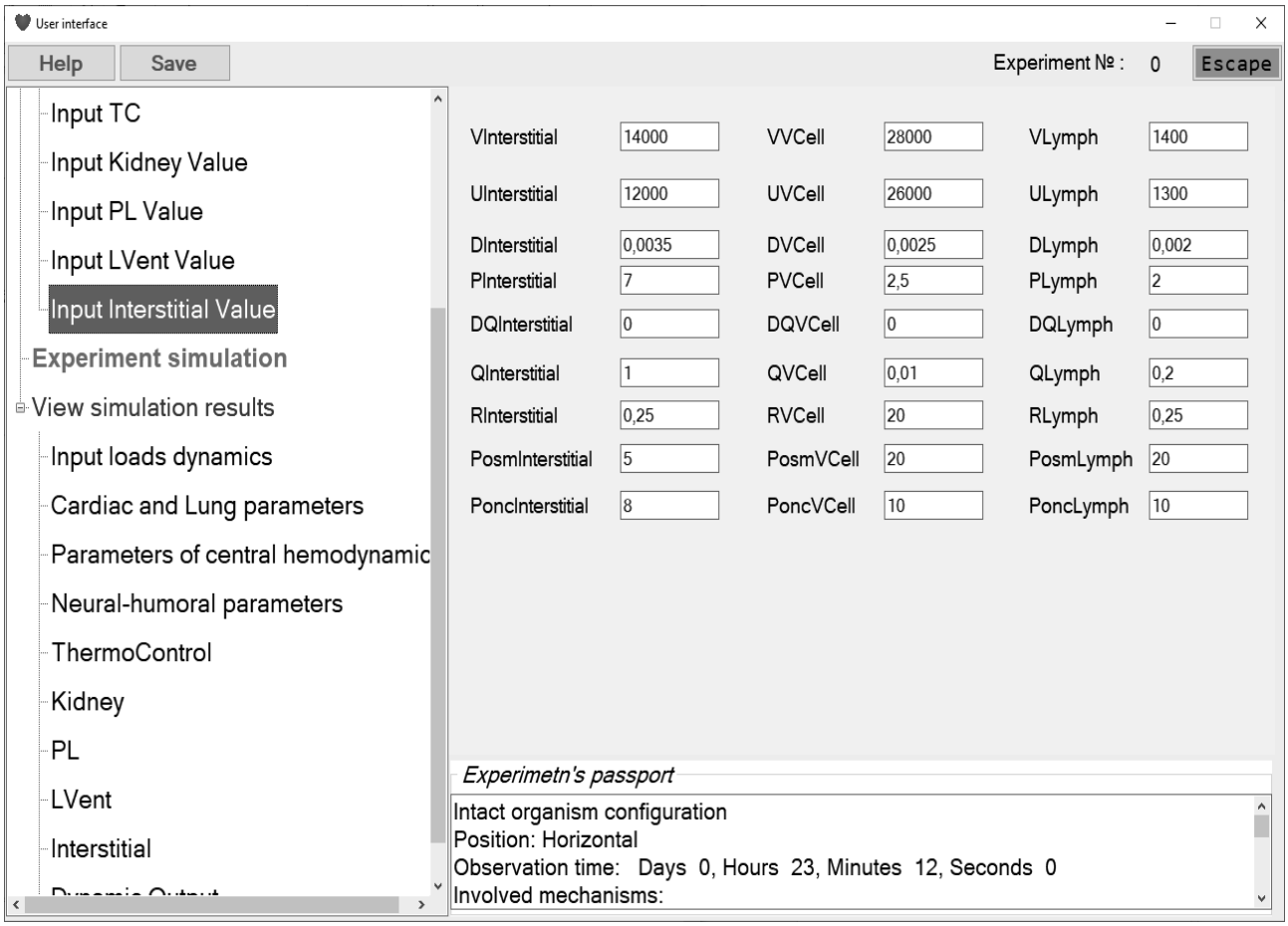

Fig. 2. A fragment of the user interface illustrating the window form for actualizing values of intercellular, cellular, and lymphatic compartments of the model before starting a simulation

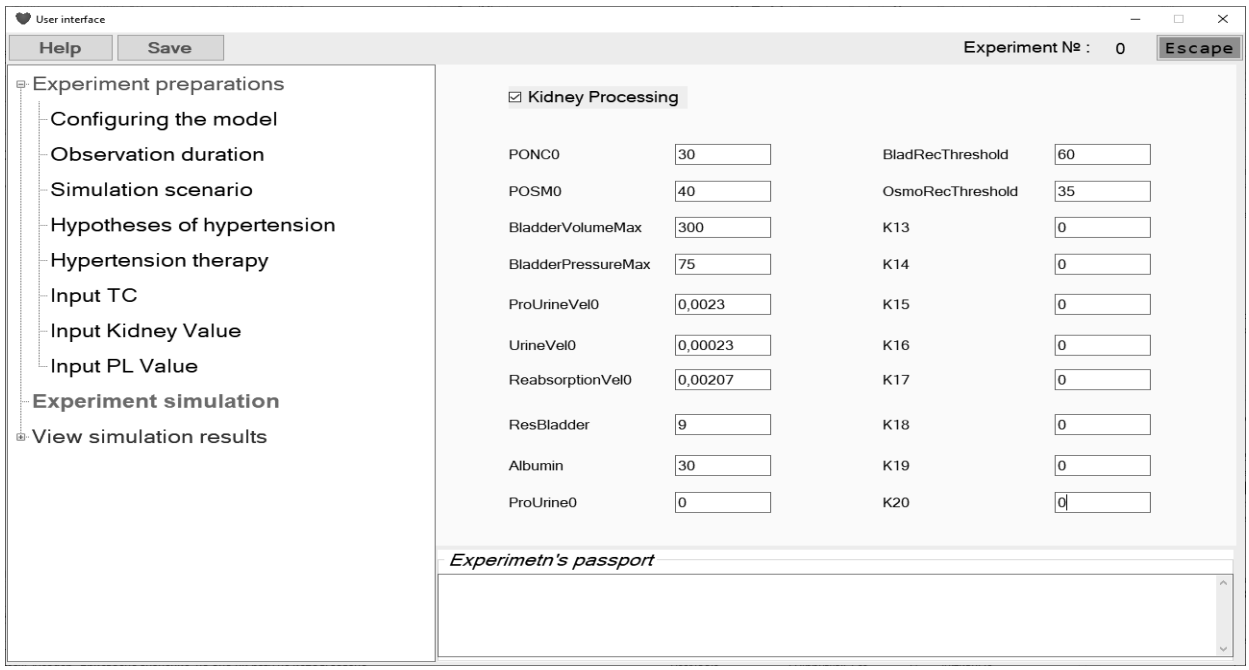

Fig. 3. A fragment of the user interface illustrating the window form for actualizing values of the kidney and bladder models before starting the simulation

Figures 4-12 illustrate several results of a computer simulation. The simulation scenario includes the following: 1) the human body position is horizontal; 2) neural and hormonal regulators controlling the function of CVS are switched on; 3) brain neurons reacting to alterations of liquor's osmotic pressure are switched off; 4) concentrations of atmosphere gases are in the norm; 5) within 24 hours period of observation the light intensity alters with the 12-hour day/night period starting from 6 hours of the morning; 6) air temperature, humidity, wind speed have the fixed dynamics; 7) serotonin and melatonin hormones display normal circadian dynamics.

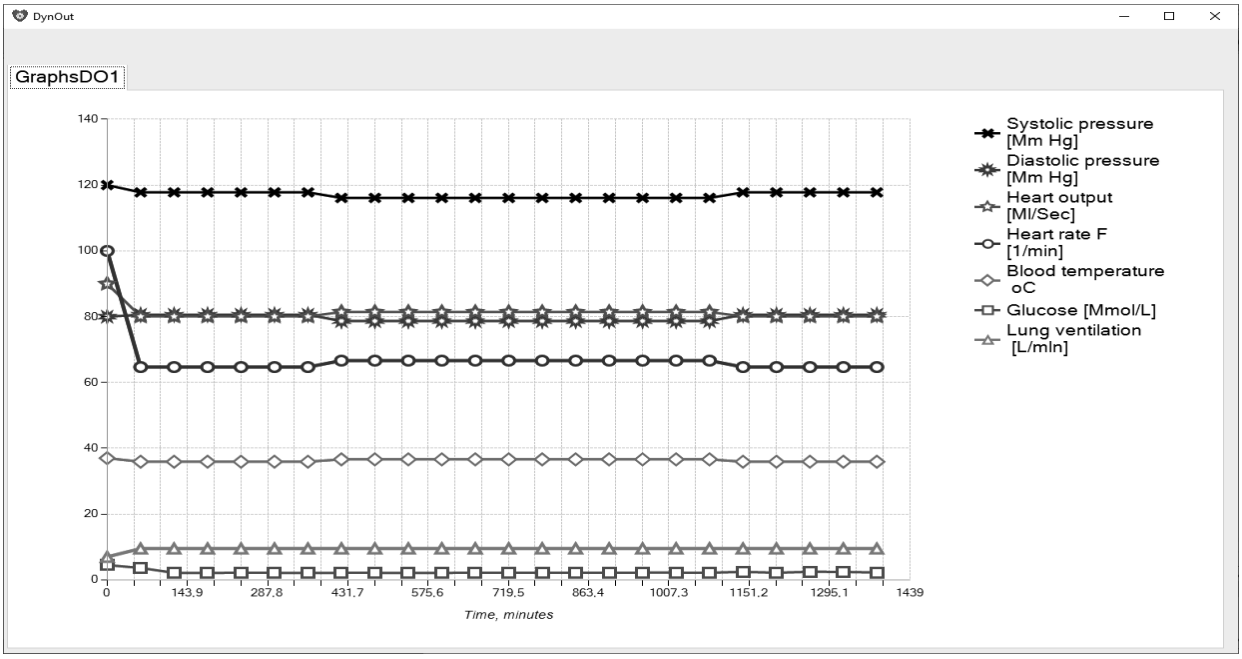

Fig. 4. Seven biological characteristics that can be specially displayed during calculations (the user arbitrarily sets intervals for every next time point)

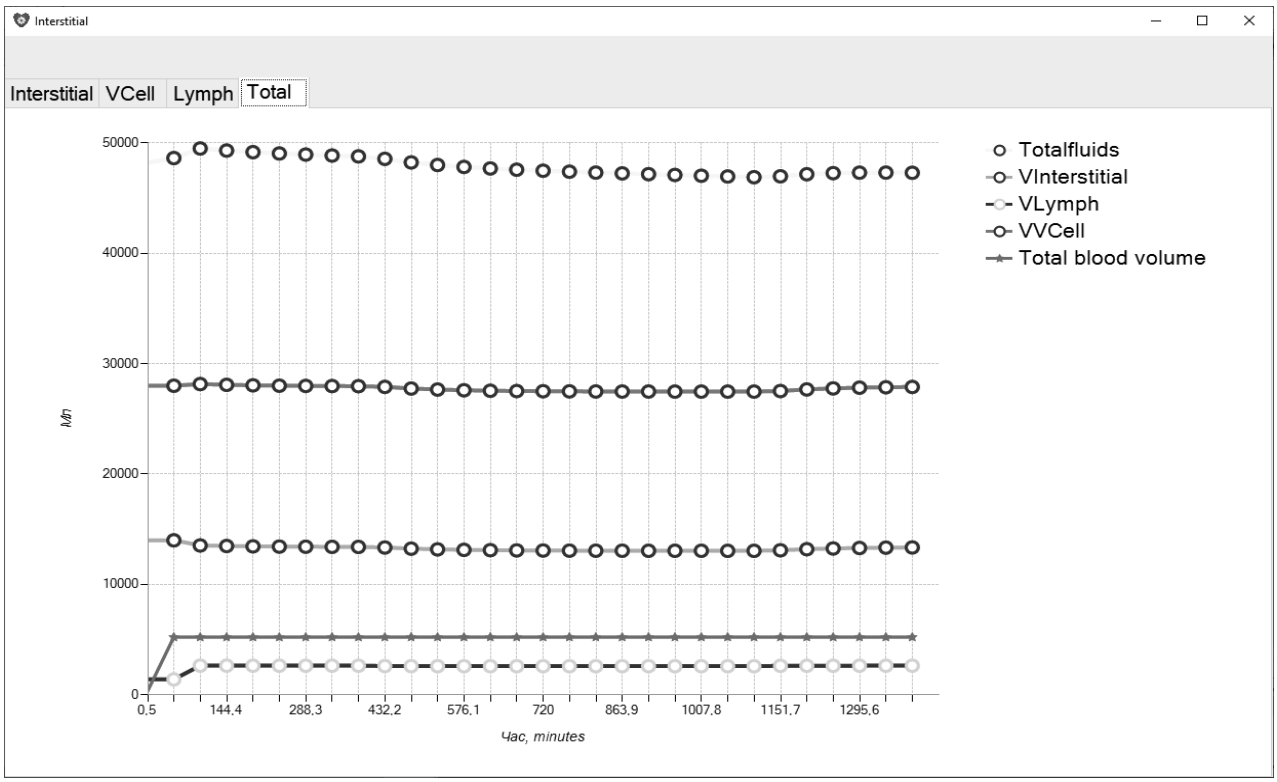

Fig. 5. The dynamics of body fluids (total and in four compartments). The simulation scenario provides a 24-hour experiment under natural dynamics of environmental temperature and lightness without activating the brain receptors of osmotic pressure

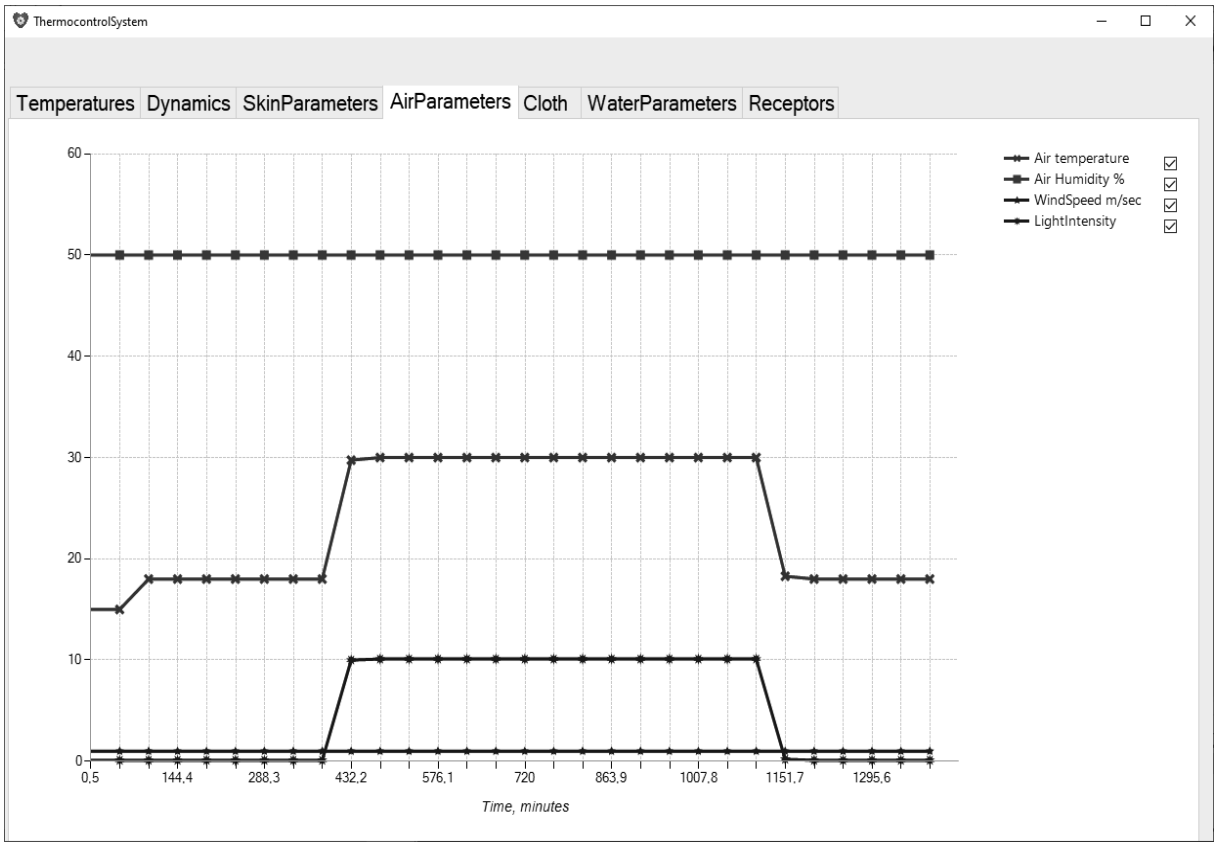

Fig. 6. Simulated dynamics of air parameters

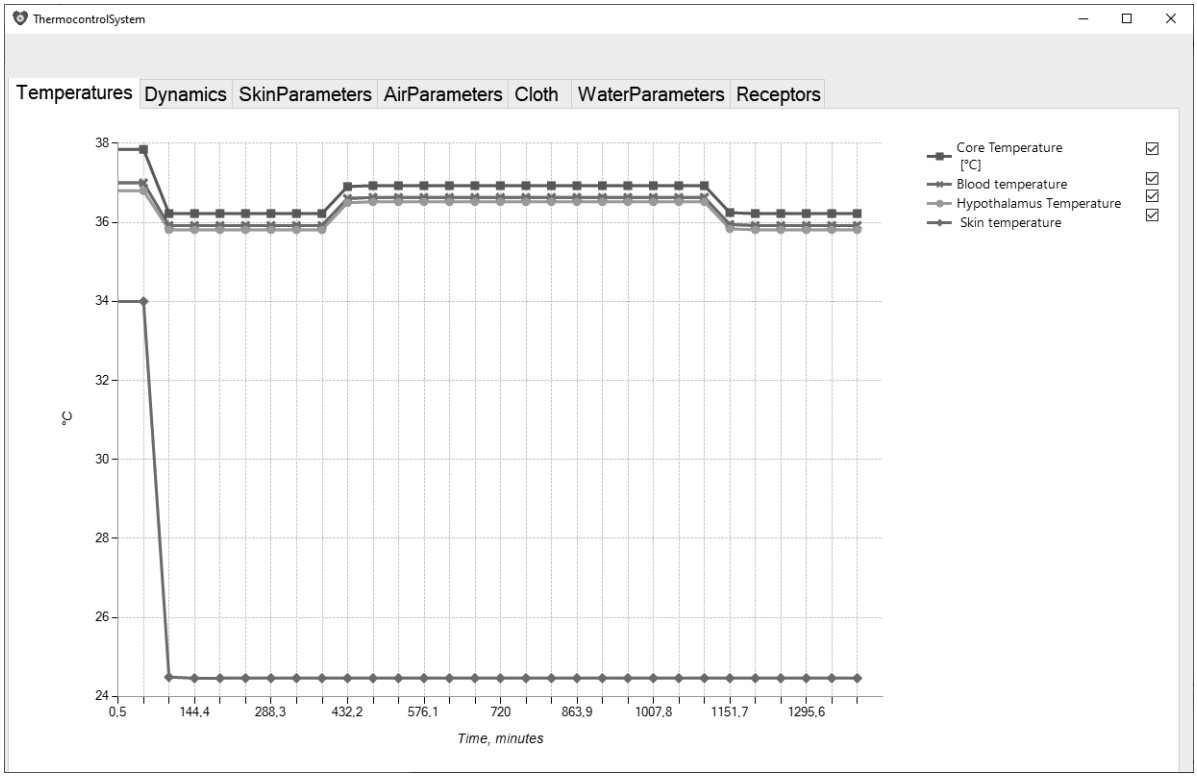

Fig. 7. Simulated dynamics of body temperatures according to the model of thermoregulation

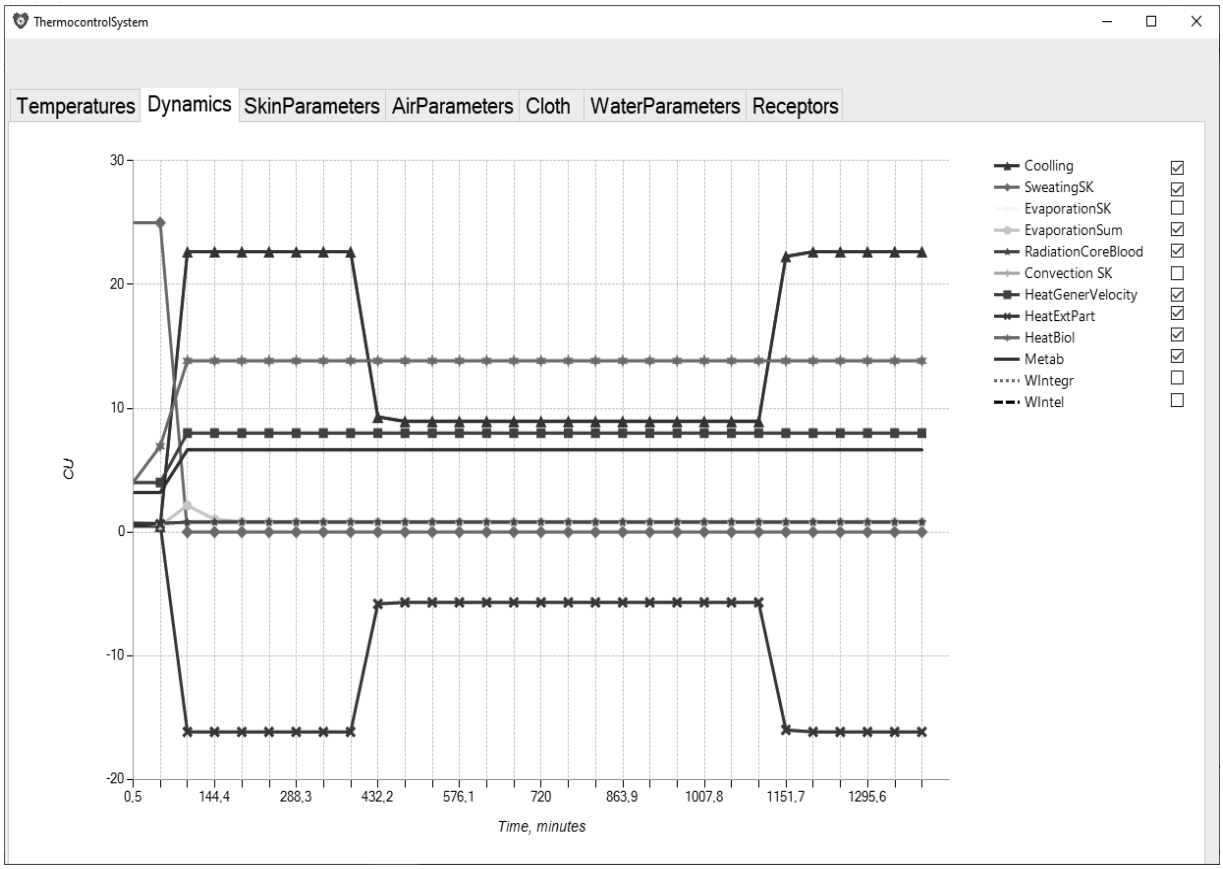

Fig. 8. Simulated dynamics of additional characteristics according to the model of thermoregulation

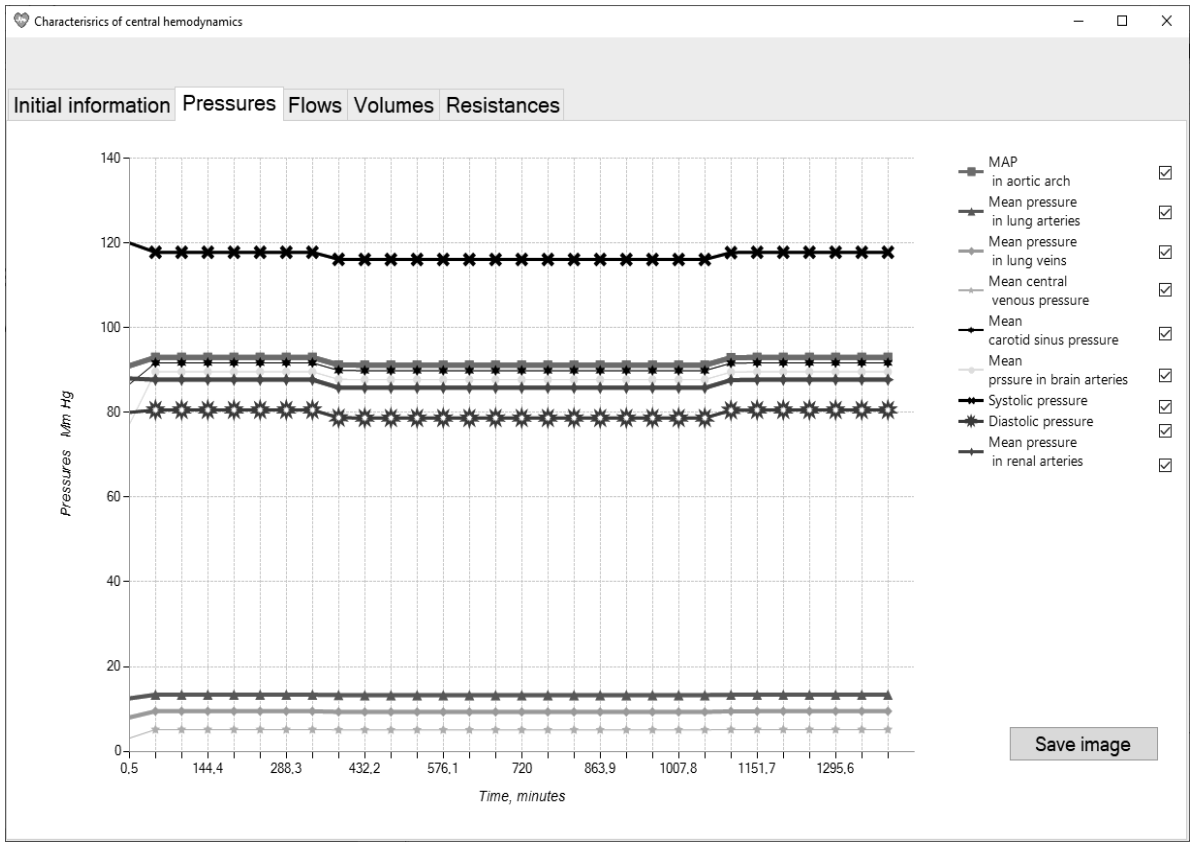

Fig. 9. Simulated dynamics of several cardiovascular characteristics

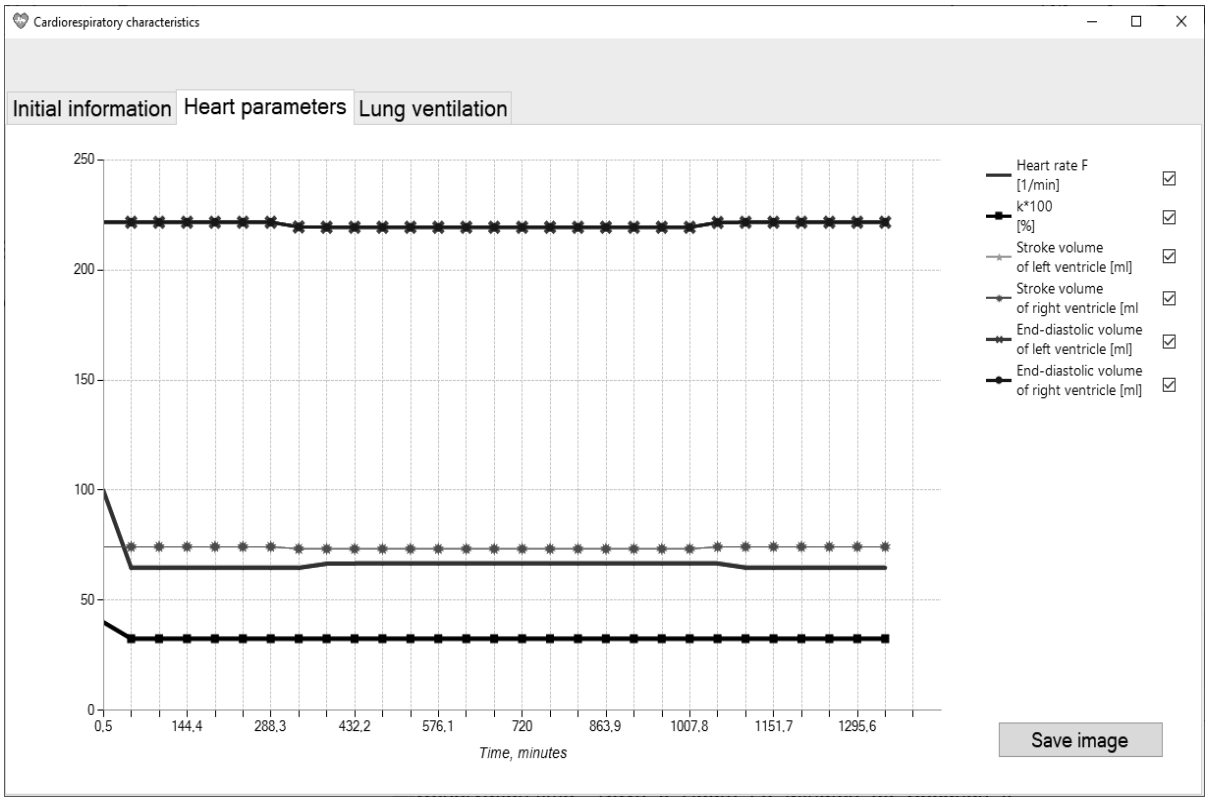

Fig. 10. Simulated dynamics of additional cardiovascular characteristics

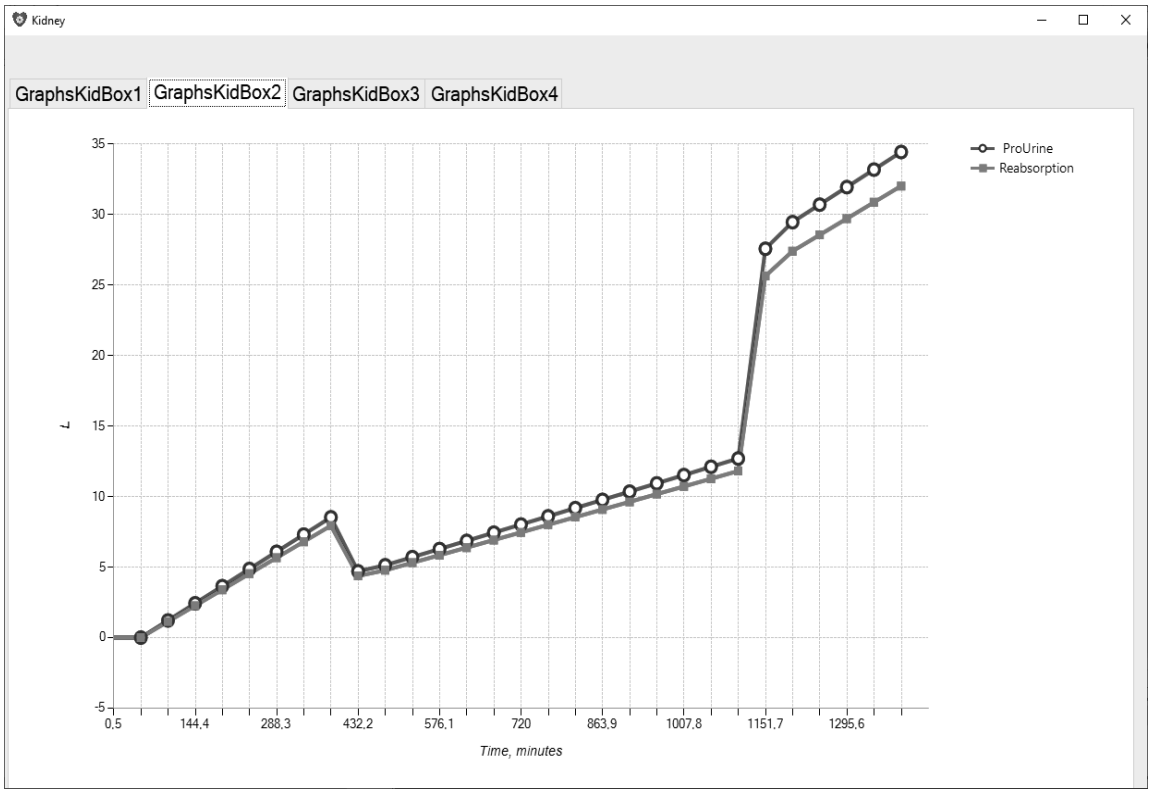

Fig. 11. Simulated dynamics of the kidney model demonstrating the difference between the production of the primary urine and its partial reabsorption

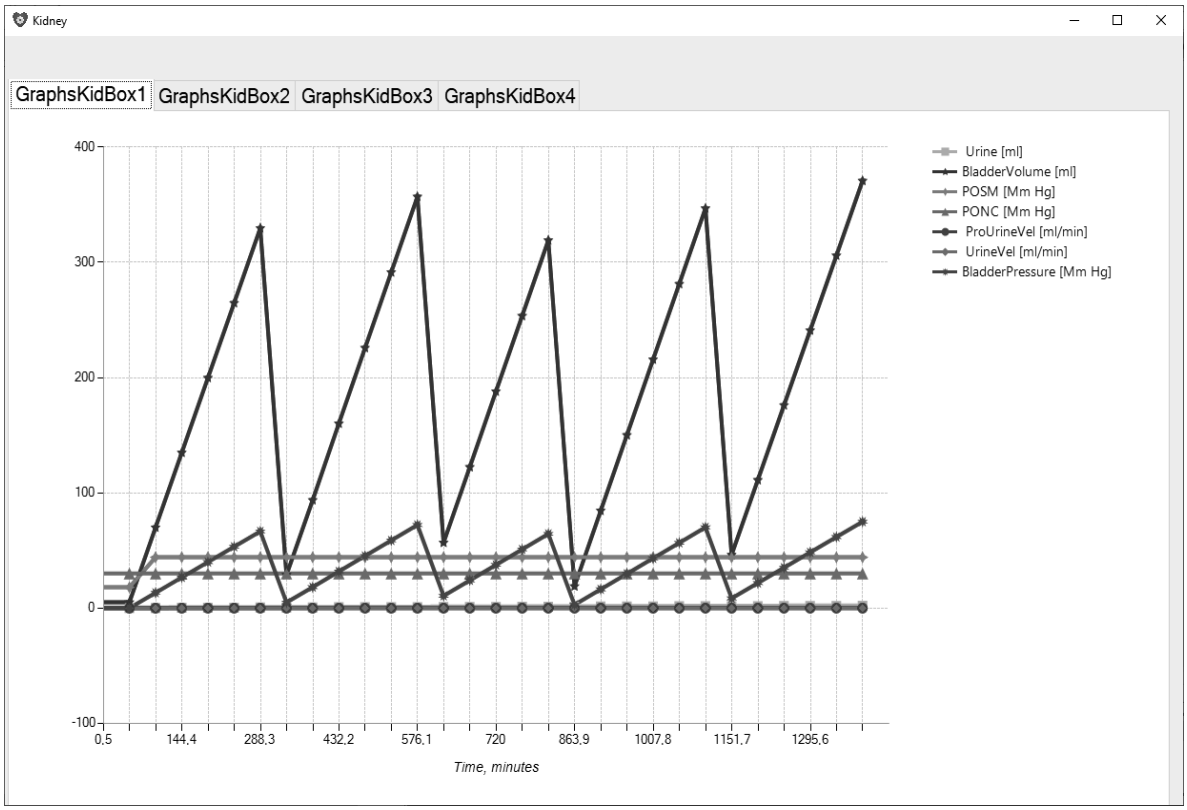

Fig. 12. Simulated dynamics of the kidney-bladder model demonstrating periodical fillings and emptying of the bladder per day (changes in hormonal activity taken into account)

Discussion

Our models are based on fundamental physiological knowledge including quantitative data like those presented in [2,3,11,12,16]. It was also critically analyzed the experience of colleagues [13-17]. Certainly, not every model constant is strongly verified. At the same time, such parameters were varied in some ranges to estimate their potential role in system-scale incorrectness. Results illustrated in Fig.4 – Fig.12 are only part of the information provided by our current software-modelling tool. It can simulate more thinkable scenarios and yield essentially more physiological output data. However, our current purpose was mainly to demonstrate the usability of the simulator. We plan to publish physiological aspects in biomedical journals. Before doing it, we aimed to thoroughly test every component model and the whole simulator using much more empirical data. Besides, the final user interface will be advanced to become maximally friendly for physiologists and physicians. We think that the fact that such a complex research tool has already been developed is an essential step forward.

Conclusion

For the first time, a special software-modeling tool (simulator) capable of essentially widening and deepening research opportunities of modern human physiologists and medics-researchers was developed. The main models, software units and the entire simulator had been mainly tested for the most well-known test scenarios. In addition to a big list of standard scenarios, the simulator provides the user with easy algorithms for constructing and simulating new scenarios. The simulator is the lonely research tool for obtaining novel data concerning the interaction of human organs that optimize cells' metabolism.

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