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A SIMULATOR PROVIDING THEORETICAL RESEARCH OF HUMAN INTEGRATIVE PHYSIOLOGY

Traditional (empiric) methodology based on direct measurements of fragmentary biological data limits the research of human integrative physiology (IP). Even assistant research based on animal experiments operates with fragmentary data. Therefore, IP's current concepts, not covering many aspects of IP's complex dynamics, cannot explain pathophysiological transformations that finally lead to non-trivial diseases. This methodological dead-end requires alternative research technology. This article presents a technology and software (*SimHIP*), widening the research potential in the area of human IP. The technology is based on two novelties. The first one is the physiological concept of a functional super-system (FSS) that optimizes cells' life despite environmental instabilities. The second novelty is the mathematical model (MM) of FSS. Fragments of MM were separately created and tuned using test scenarios. *SimHIP* integrating these fragments provides the physiologist-researcher with an intuitive interface to: a) construct a simulation scenario; b) execute the simulation; c) visualize input-output physiological dynamic dependencies for every chosen combination; and d) save every simulation data for future considerations and publications. *SimHIP* is an autonomous C# software provided as an Exe module for IBM-compatible computers. Medical students can be additional users of *SimHIP*.

Keywords: organs, physiological systems, mathematical model, visualization, students

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СИМУЛЯТОР ДЛЯ ПРОВЕДЕННЯ ТЕОРЕТИЧНИХ ДОСЛІДЖЕНЬ ІНТЕГРАТИВНОЇ ФІЗІОЛОГІЇ ЛЮДИНИ

Традиційна (емпірична) методологія, заснована на прямих вимірюваннях фрагментарних біологічних даних, обмежує дослідження інтегративної фізіології (ІФ) людини. Навіть допоміжні дослідження, що базуються на експериментах з тваринами, оперують фрагментарними даними. Тому сучасні концепції ІФ, не охоплюючи багато аспектів складної динаміки ІФ, не можуть пояснити патофізіологічні трансформації, які зрештою призводять до нетривіальних захворювань. Цей методологічний глухий кут вимагає альтернативної дослідницької технології. У цій статті представлено технологію та програмне забезпечення (*SimHIP*), що розширюють дослідницький потенціал в галузі ІФ людини. Технологія базується на двох новинках. Перша - фізіологічна концепція функціональної суперсистеми (ФНС), яка оптимізує життя клітин, незважаючи на нестабільність навколишнього середовища. Друга новинка - математична модель (ММ) ФНС. Фрагменти ММ були окремо створені та налаштовані за допомогою тестових сценаріїв. *SimHIP*, інтегруючи ці фрагменти, надає фізіологу-досліднику інтуїтивно зрозумілий інтерфейс для: а) побудови сценарію моделювання; б) виконання моделювання; в) візуалізації фізіологічних динамічних залежностей вхід-вихід для кожної обраної комбінації та г) збереження всіх даних моделювання для майбутніх розглядів та публікацій. *SimHIP* — це автономне програмне забезпечення на C#, що постачається як Exe-модуль для IBM-сумісних комп'ютерів. Студенти-медики можуть бути додатковими користувачами *SimHIP*.

Ключові слова: органи, фізіологічні системи, математична модель, візуалізація, студенти

Introduction

Medical prophylactic, diagnostic, and treatment technologies are based on the physiological concepts of norm, homeostasis, and adaptation. These concepts generally proposed to explain biophysical, biochemical, and physiological mechanisms evolutionarily appeared to survive an organism in unstable living environment. Modern biology advanced this fundamental knowledge including genetic aspects. However, a lot of diseases, in particular those associated with age, are still non-trivial to be timely diagnosed and cardinally cured. The current medicine is compelled to fight with such diseases only using palliative cure mitigating the pain and patient’s suffering until painkillers are taken. Methodological limitations, playing a significant role in the current situation enormously arise, if the organism is considered as a specific community of specialized cells forced to exist despite casual or regular destructive forces. The problem is that modern empirical human physiology does not have technologies that would allow simultaneous monitoring of a huge number of biological parameters at different organizational levels (cells, their colonies, specialized organs, their anatomical and functional systems, and the whole organism) of the body.

Traditional empirical biomedical research alternatively suggests experiments on model animals. But even in this case, the number of vital parameters to be observed in dynamics is limited. Modern physiology and medicine have found themselves in a methodological impasse, so the search for a way out of it is encouraged.

One of the promising areas that can enhance empirical data with computational data is the method of mathematical modeling. Typically, human physiology models have been developed to simulate the function of a single organ (e.g., heart [1], lungs [2], liver [3], pancreas [4], and kidneys [5]) or an anatomical system (e.g., cardiovascular system [6] and digestive system [7]) under given changes in input variables. Often, the purpose of such models is applied: to calculate ranges of values for unmeasured characteristics. Additional model types that offer a better understanding of certain intricate aspects of life mechanisms have been created. Theoretically, modeling could significantly deepen the understanding of human integrative physiology (IP). The required model must quantitatively describe the mechanisms that facilitate the interaction of human internal organs co-evolved to optimize cell physiology. The general biological concept, known as the concept of functional super-systems (FSS), which explains the main principles of organ interaction, is described in [8]. The concept of FSS sheds new light on interactions of internal organs and underlines the fundamental role of intracellular regulator mechanisms in the origin of fluctuations and trends of human physical health. Specialized mathematical models of organs and anatomical-functional systems, which interact to optimize cell physiology despite environmental destructive alterations, have been developed, tested under physiological conditions, and published [9-10]. These publications also contain information about simulation algorithms and specific software modules.

The goal of this presentation is to demonstrate the main potentials of the specialized software-modeling tool (***SimHIP***) in research of human FSS.

The main purpose of *SimHIP*

SimHIP is an autonomous .exe module developed in C# environment. The complex quantitative mathematical model of human FSS is a system of differential equations (SDE) that describes the dynamics of FSS. Algorithms provide approximate solution of SDE for given initial conditions and dynamics of input variables.

SimHIP’s main purpose consists in providing the physiologist with an unconventional assistant research technology that allows obtaining new quantitative knowledge about the dynamics of human internal organs’ interaction under conditions of a wide range of artificially created internal/external changes. The knowledge can be obtained by providing a single computer experiment. Procedures required to prepare such an experiment and to analyze its results are provided by the user interface (UI). Before considering UI in more detail, it is worth saying some words about simulation scenarios.

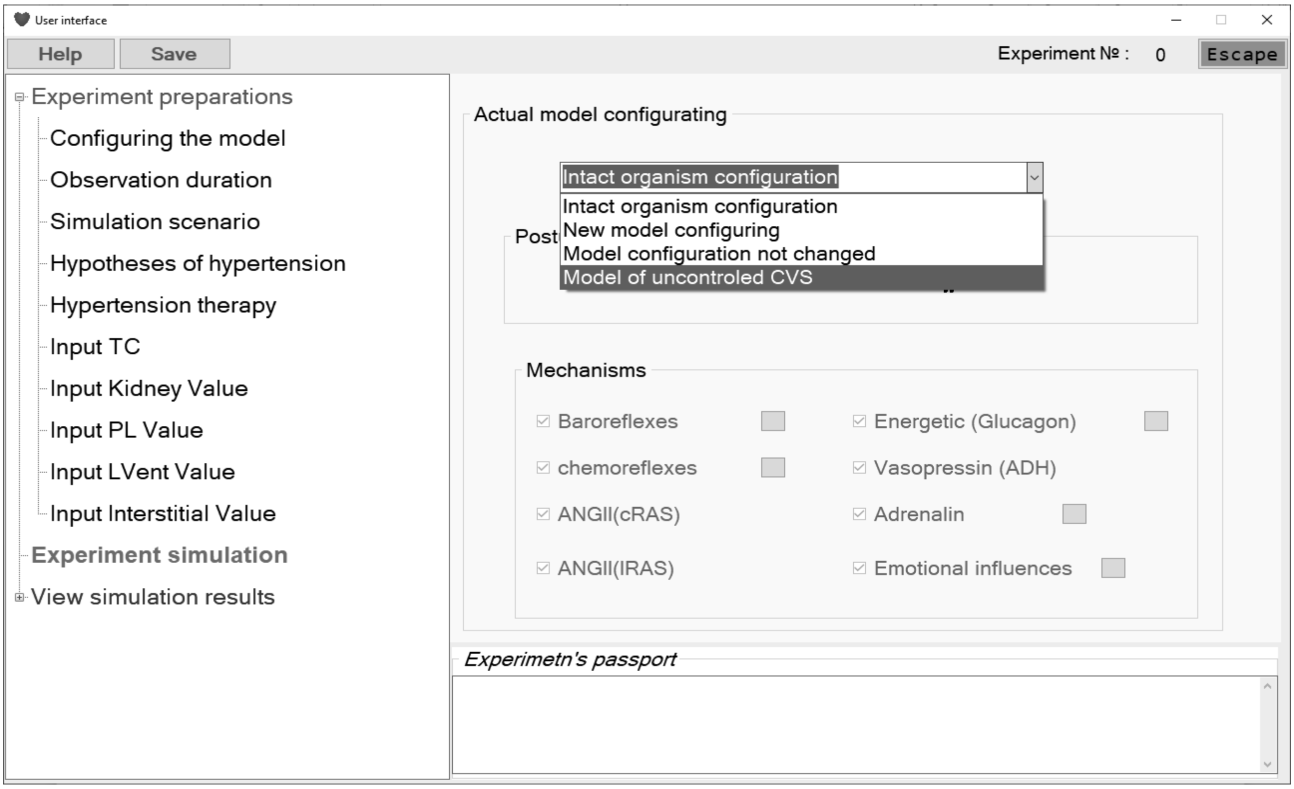
Simulation scenarios presented in a pop-up window of UI include:

- **The default scenario of test simulation.** It is provided for the intact human organism for the body horizontal position. The user does not moderate any model parameter. In our models, not every parameter is ideal; thus, just after calculation is started, a transitory process begins. It is empirically set that transitions are mainly over within several minutes of modeled time, and a practically steady-state physiological mode is reached. *SimHIP* informs about calculation finishing and provides access to simulation results. The user can look at up to 58 graphs characterizing physiological dynamics of mean man life variables within the 10 minutes.

- **New model configuring.** By choosing this alternative, the user becomes able to re-combine model modules, actualize values of their constants, and the simulation scenario. The same up to 58 output data are assessable for every simulation scenario. The actualization if desirable concerns every component model listed in the main interface.

The user interface of *SimHIP*.

The main screen form of the user interface (UI) is presented in Figure 1. As one can see, the actualization concerns parameters of models representing the thermoregulatory system (TC), the kidneys, the pancreas-liver interaction (PL), the lung ventilation (LVent), and interstitial compartments’ interaction. As the model of cardiovascular system (CVS) is in the focus of our complex model, mechanisms controlling CVS have been



Experiment № : 0

Intact organism configuration

☑ Baroreflexes ☐

☑ chemoreflexes ☐

☑ ANGII(cRAS)

☑ ANGII(IRAS)

☑ Energetic (Glucagon) ☐

☑ Vasopressin (ADH)

☑ Adrenalin ☐

☑ Emotional influences ☐

Fig. 1. The main screen form for actualizing the basic model.

The actualization concerns parameters of thermoregulatory system (TC), kidneys, pancreas-liver interaction model (PL), lung ventilation model (LVent), model of interstitial compartments, as well as mechanisms controlling the cardiovascular system. Special options provide actual parameters of observation, Simulation scenario, Hypotheses of hypertension and its therapy. Special option “Experiment simulation” starts the computer experiment. Just after the experiment is over, the option “View simulation results” opens access to graphical simulation results.

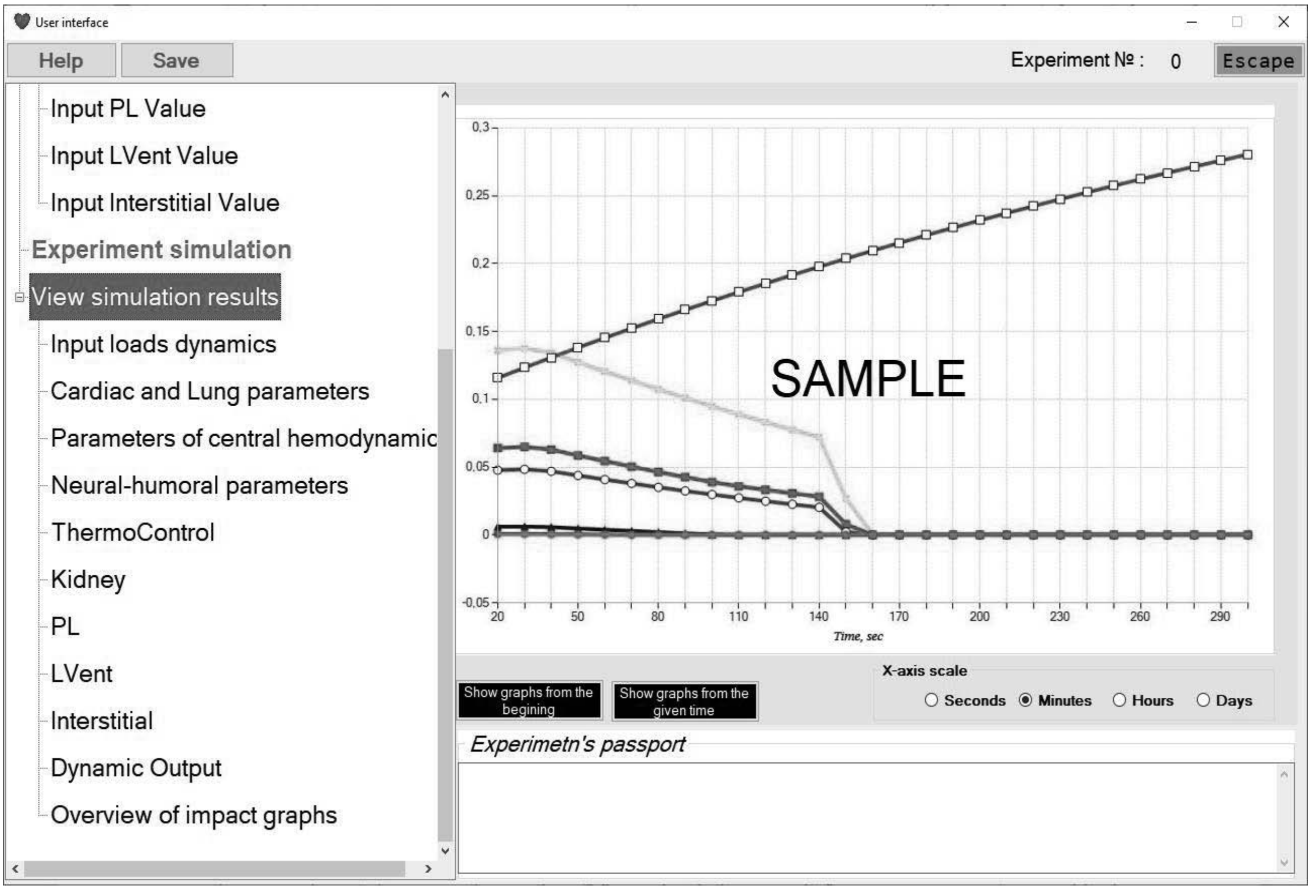


Fig. 2. The screen form of UA providing an access to results of the simulation for each model.

Graphs can be illustrated either from the beginning or from the 20th second of simulation. Depending on its duration, the user can chose appropriate time scale.

presented in UA most detailed. This concerns special options for actualization of observation parameters, simulation scenario, hypotheses of hypertension and its therapy.

Special option “Experiment simulation” starts the computer experiment. Just after the experiment is over, the option “View simulation results” opens an access to graphical simulation results.

The double windows (see Fig. 3) are the standard screen form for visualizing simulation results in graph forms. The lower window collects input variables, and the upper window collects output variables. The user can collect variables as desired and choose color or white and black lines with up to 15 specific signs. Additional boxes on the right serve as a selection of color or black and white presentation of graphs. Access to alternative clusters is opened by clicking “Choose a cluster of graphs” (an example is shown in Fig. 5).

The list of clusters contains eight clusters:

- Cardiovascular system (includes 7 variables: Systolic pressure; Diastolic pressure; Mean arterial pressure; Mean central venous pressure; Heart rate; Stroke volume of left ventricle; Heart input flow);
- Thermoregulation system (includes 9 variables: Blood temperature; Skin temperature; Air temperature; Wind speed; Air humidity; Light intensity; Blood Serotonin; Blood melatonin; Hypothalamus temperature);

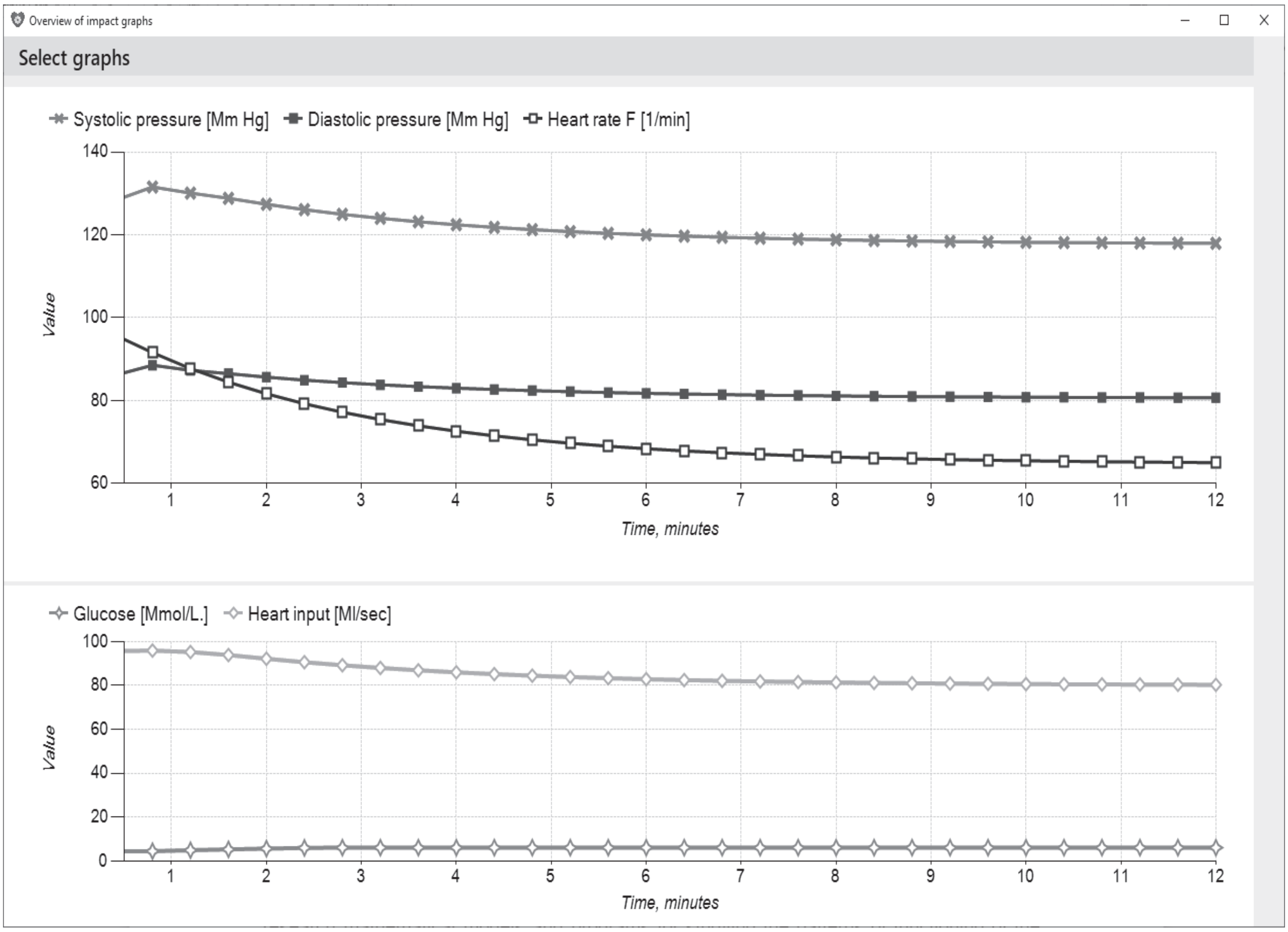


Fig. 3. A sample of typical graphs presenting the dynamics of input (bottom graphs) and output (upper graphs) variables.

By clicking "Select graphs" in the upper left corner, the user can access a special screen form to visualize graphs concerning other physiological variables completed in 7 clusters (see Fig. 4).

- Kidneys and bladder (includes 12 variables: Urine; Prourine; Urine velocity; Prourine velocity; Reabsorption; Bladder volume; Bladder pressure; POSM; PONC; Osmoreceptors; Bladder receptors; Sodium);

- Pancreas-Liver (includes 4 variables: Insulin; Glucose; Glucagon; Glycogen);

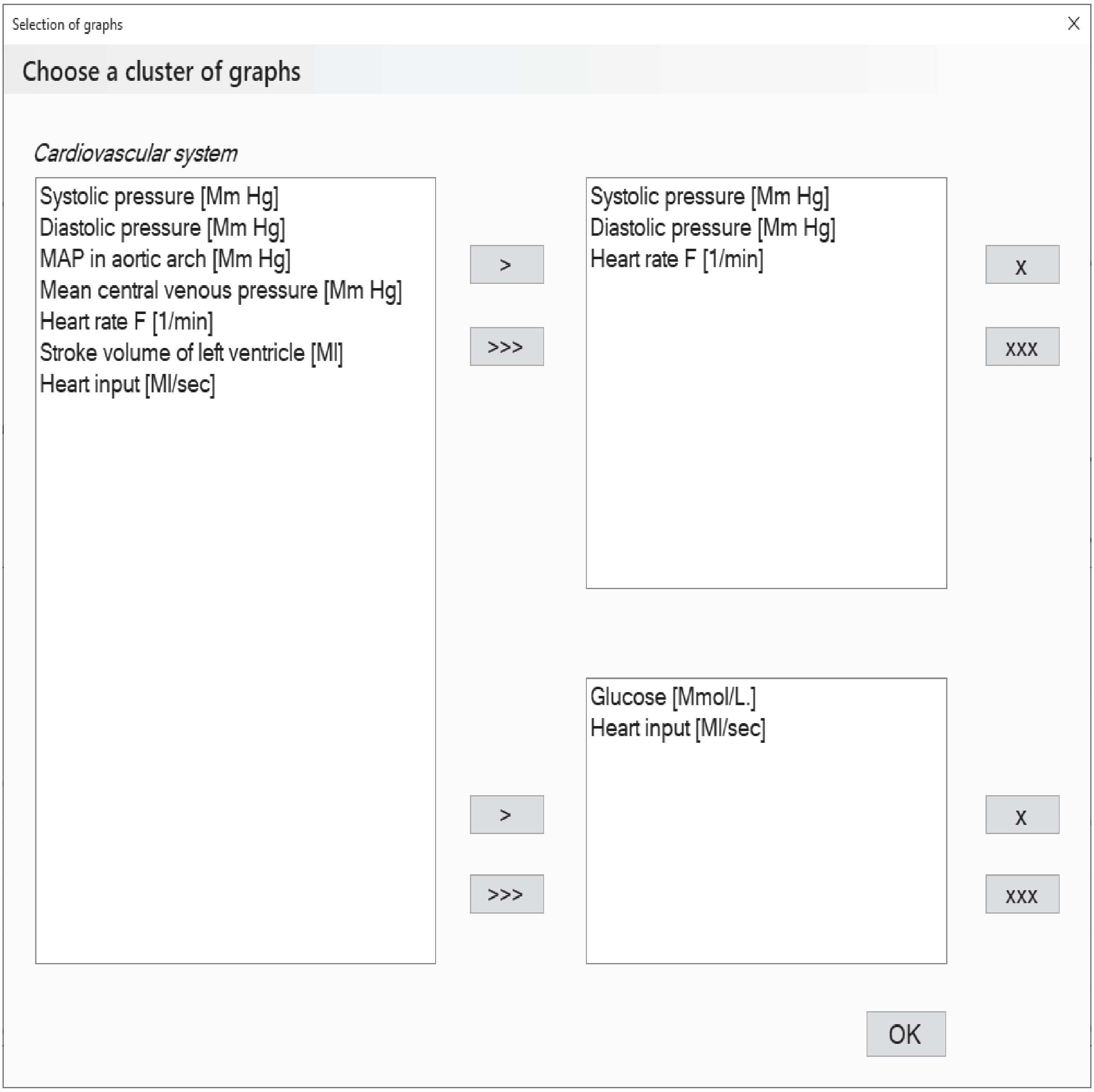
- Pulmonary ventilation (includes 4 variables: PaO_2; $PaCO_2$; pH; Lung ventilation);

- Liquid compartments (includes 8 variables: Total blood volume; Summary blood volume in arteries; Summary blood volume in veins; Total long blood volume; Total fluids; Interstitial volume; Total intracellular volume; Lymph volume);

- Indicators of neuroendocrine system (includes 9 variables; Summary baroreception; Chemoreception; Heart sympathetic nerve activity; Heart parasympathetic nerve activity; Vascular sympathetic nerve activity; Renin; ANG2; Adrenalin; Vasopressin);

- Indicators of condition (includes 5 variables: Aerobic exercise; Degree of table tilt; Resistance of renal afferent arteries; Resistance of coronary arteries; Resistance of brain arteries).

So, the current version of ***SimHIP*** provides the physiologist with the dynamics of 58 biological variables. However, the complex model consists of a larger amount of biological data. Some of these data concern the initial parameters (constants) used in the



Selection of graphs

Choose a cluster of graphs

Cardiovascular system

Systolic pressure [Mm Hg]
Diastolic pressure [Mm Hg]
MAP in aortic arch [Mm Hg]
Mean central venous pressure [Mm Hg]
Heart rate F [1/min]
Stroke volume of left ventricle [Ml]
Heart input [Ml/sec]

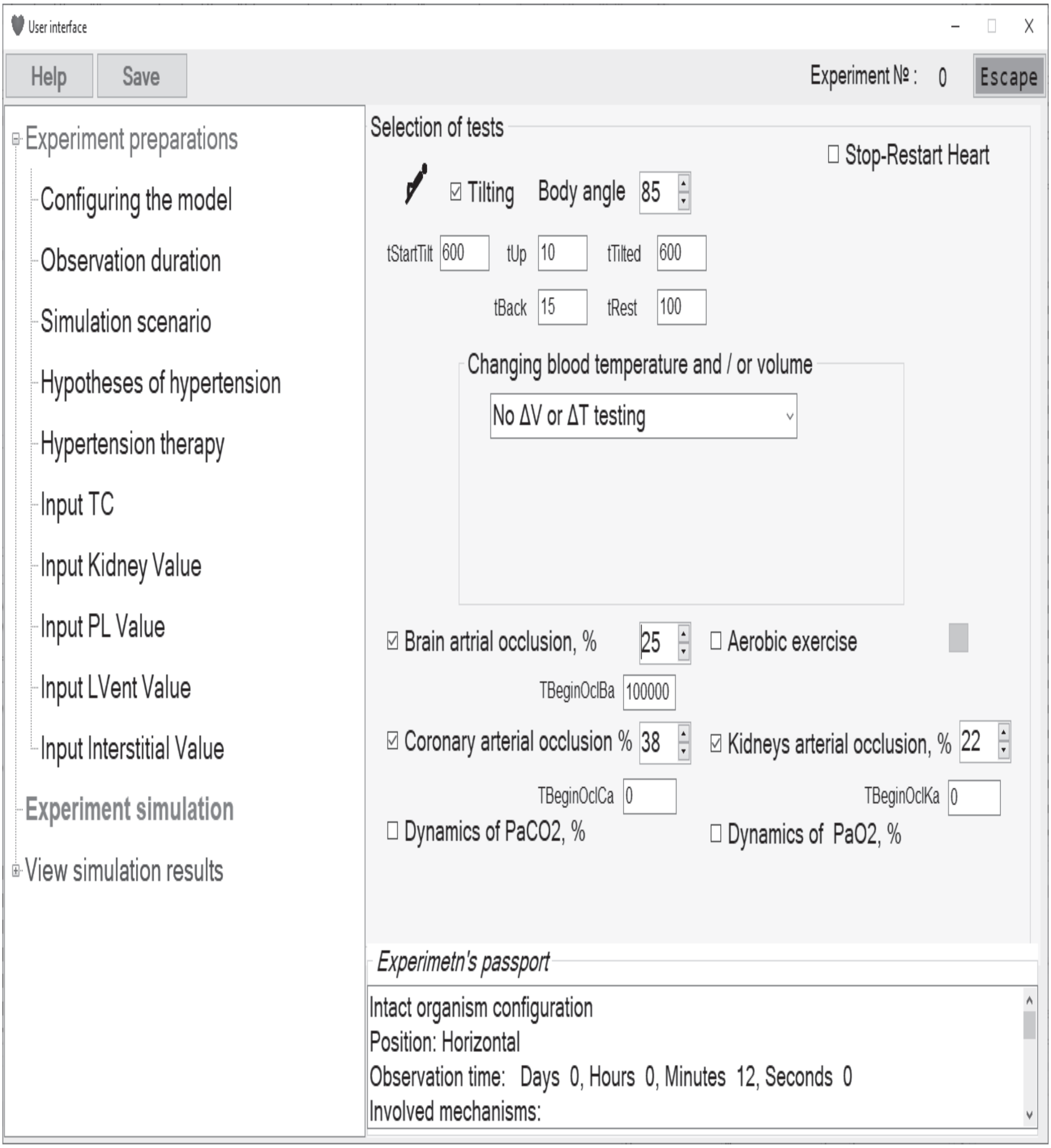
Systolic pressure [Mm Hg]
Diastolic pressure [Mm Hg]
Heart rate F [1/min]

Glucose [Mmol/L.]
Heart input [Ml/sec]

Fig. 4. The service window “Choose a cluster of graphs” provides two functions: a) configuring input (output) variables in the frame of active cluster of graphs; b) choosing a new cluster from the list of clusters for providing the function a).

mathematical models. Although these constants were chosen through thoroughly tested tunings, ***SimHIP*** proposes special options to advanced users: they can vary constants, execute a simulation, and watch the physiological consequences of every alteration.

Fig. 5 special presented to illustrate how the user activated the stroke **Simulation sce nario** in left light window does set additional parameters of the chosen test. This case the tilting on 85° upright does start at 600th seconds of initial horizontal position. The table turns head-up with a person's head in 10 seconds, the person is in an inclined position for 600 seconds, after which in 15 seconds the table is returned in horizontal and the tested person continues to be in the rest state for 100 sec. Note that additional parameters (the resistances of



Experiment №: 0

☐ Stop-Restart Heart

☑ Tilting Body angle 85

tStartTilt 600 tUp 10 tTilted 600

tBack 15 tRest 100

Changing blood temperature and / or volume: No ΔV or ΔT testing

☑ Brain artrial occlusion, % 25 ☐ Aerobic exercise

TBeginOclBa 100000

☑ Coronary arterial occlusion % 38 ☑ Kidneys arterial occlusion, % 22

TBeginOclCa 0 TBeginOclKa 0

☐ Dynamics of PaCO2, % ☐ Dynamics of PaO2, %

Intact organism configuration
Position: Horizontal
Observation time: Days 0, Hours 0, Minutes 12, Seconds 0
Involved mechanisms:

Fig. 5. Preparing a simulation of a postural test in combination of partial occlusions of coronary, brain, and kidneys arteries. Simulation results are presented in Fig. 6 and Fig. 7.

brain, coronary, and kidney arteries) have also been actualized.

At the bottom part of this window, the special scrolling window is shown. It collects additional information about the computer experiment.

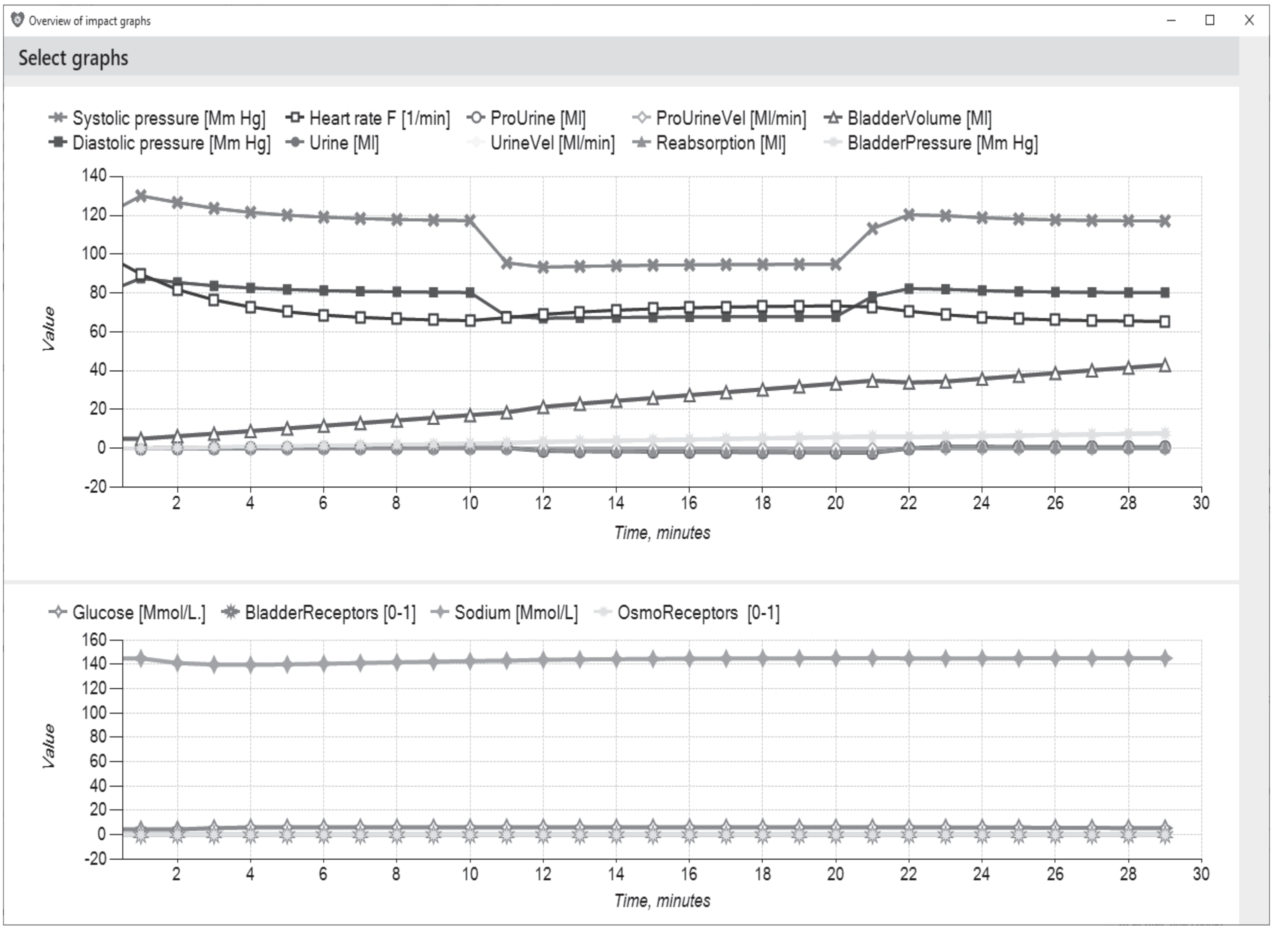
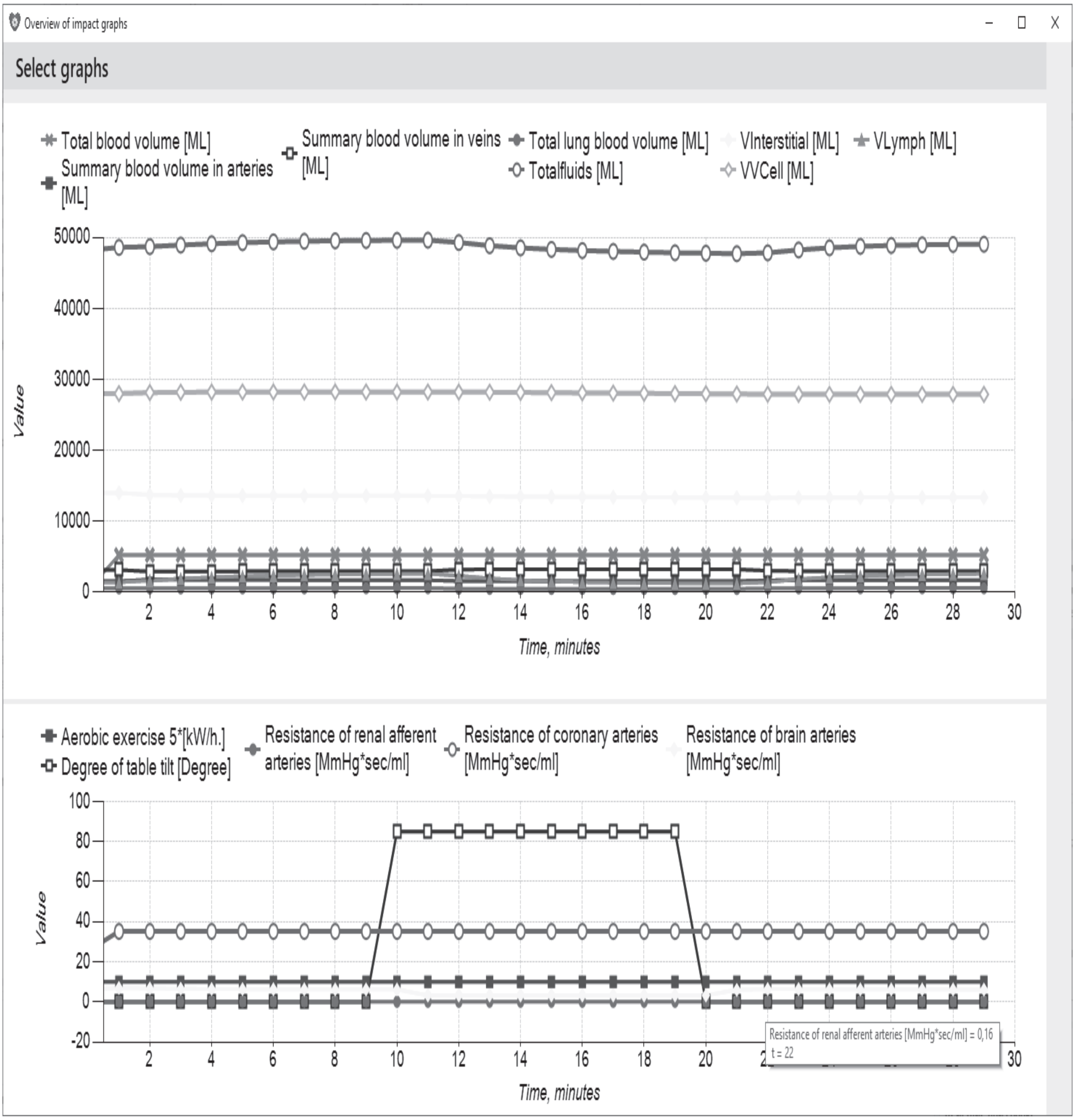


Fig. 6. The dynamics of chosen physiological data under simulation of the scenario described in Fig. 5.

Discussion

The research technology proposed by "*SimHIP*" is an unusual solution to physiological problems. Both physiologists and medics are more used to working with devices that provide them with measurements of life characteristics necessary to make more reliable conclusions. Such a device usually provides one or two an additional biological characteristics. Examples of such medical devices are the electrocardiograph, echocardiograph, electroencephalograph, and others. Even famous devices that provide magnetic resonance imaging can deal with one variable – biological liquid (blood) volume in local body areas. Our *SimHIP* deals with 58 dynamic characteristics. Certainly, cannot use initial data measured in a person. However, *SimHIP* is an exclusive research tool assisting the human physiologist to minimize likely mistakes concerning the multiscale integrative functioning of human organisms. In this sense, simulations seem to be the cheapest way to avoid false conclusions, including those concerning principles determining the non-trivial pathophysiological transformations. Another promising aspect of the use of our *SimHIP* is the process of teaching future doctors the basics of physiology. Until now, diagrams and pictures depicting the anatomy and simplified physiology of organs have been the main way of presenting knowledge about how the body functions. Meanwhile, there is still no solid fundamental knowledge about how internal organs quantitatively interact. In this regard, our simulator is the first software product that offers to restructure the process of training future doctors so that each student can see with his own eyes the consequences of the changes he makes to the model of a specific organ.



Resistance of renal afferent arteries [MmHg*sec/ml] = 0,16
t = 22

Fig. 7. The dynamics of other chosen physiological data under simulation of the scenario described in Fig. 5.

Conclusion

For the first time, a concept has been created and a computer program has been developed that is oriented towards use by a physiologist who studies the patterns of integrative physiology of human cell life support in an unstable environment. Based on a complex mathematical model of the interaction of internal organs, the program is designed as a specialized autonomous simulator, *SimHIP*. It can be used by both research physiologists and future doctors when teaching the basics of human physiology.

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