

# INTEGRATED MATHEMATICAL MODEL FOR IMITATION OF THE COURSE OF VIRAL DISEASE AND CORRECTION OF THE INDUCED HYPOXIC STATE

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The aim of the work was to create a complex mathematical model simulating the course of the disease caused by the SARS-CoV-2 virus on the level of interaction between functional systems of organism and pharmacological correction of organism hypoxic states arising in the complicated course of the disease. In the present work the methods of mathematical modeling and theory of optimal control of moving objects were used. The proposed integrated mathematical model consisted on the mathematical models of functional systems of respiration and blood circulation, thermoregulation, immune response, erythropoiesis, and pharmacological correction. Individual patient data were taken for this model, and the disturbing effect in the form of viral disease was simulated. The reactions of functional respiratory and blood circulatory systems were predicted. Partial pressures of respiratory gases in alveolar spaces and their tensions in lung capillaries blood, arterial and mixed venous blood, and tissue fluid were calculated. Further the intravenous injection of antihypoxant was simulated and the values of the same parameters were calculated. In such a way it was possible to choose the most optimal way of hypoxic state correction for any individual. This model is theoretical only for today because the models of respiratory and blood circulation systems were designed for the average person and it does not suppose peculiarities of individual persons infected with SARS-CoV-2. In particular, this concerns the peculiarities of gas exchange in the alveolar space and characteristics of respiratory gases diffusion through the alveolar-capillary and capillary-tissue membranes. However, it is one of possible directions for solving the complex tasks related to treatment of the disease caused by SARS-CoV-2 virus. In the result of the work the complex of information support for the imitation of viral disease course was developed at the level of interaction of organism functional systems, as well as pharmacological correction of caused by it hypoxic states.

**Key words:** SARS-Cov-2 virus, immune response model, mathematical model of the respiratory system, hypoxic state, infection lesion

New coronavirus infection burst had happened in Republic of China with epicenter in Wuhan (Hubei Province) in late 2019. The World Health Organization officially named it COVID-19 (“Corona virus disease 2019”) on February 11, 2020. The International Committee on Viruses Taxonomy had assigned the official name to the agent of this infection — SARS-CoV-2 on February 11, 2020.

The information on epidemiology, clinical features, prevention, and treatment of this disease is limited until now. The most common clinical manifestation of the new variant of coronavirus strain infection was bilateral pneumonia: the development of acute respiratory distress syndrome was registered in 3–4% of patients [1]. This potentially severe acute respiratory infection causes dangerous disease [2]. It can occur both in the form of

acute respiratory viral infection with mild course [3, 4] and in severe form with such specific complications as viral pneumonia caused acute respiratory distress syndrome or respiratory failure with a risk of the death [5]. However, full clinical picture is not yet clear [6]. There are no specific antiviral agents for the treatment or prophylaxis of this disease [7]. In most cases (approximately 80%) it turns out that no specific treatment is required, and recovery takes place on its own [2, 8]. In severe cases, specific means and methods are used to maintain functions of vital organs [9]. Respiratory insufficiency development is also possible against the background of this infection [3]. Less than a third of patients demonstrated the development of acute respiratory distress-syndrome [2]. In case of acute respiratory distress-syndrome, tachycardia, tachypnoea or cyanosis may also be appeared to accompany hypoxia [6].

Inflammatory processes can influence on cardiovascular system resulting in arrhythmias and myocarditis. Acute heart insufficiency is mostly found in severely or critically ill patients. Infection can occur long-term influences on the health of cardiovascular system. In case of patients with cardiovascular diseases in anamnesis, strict monitoring of their conditions may be required [2].

There is no specific antiviral therapy against SARS-CoV-2 virus [9] and there is no evidence of effective immunomodulating therapy [10]. Patients receive mainly symptomatic and supportive therapy. In severe cases, treatment aims to maintain vital functions of organs [9].

Although unlicensed drugs and experimental therapies are used today in practice of coronaviral disease treatment, for example, with the use of antiviral agents, such treatment should be carried out within the framework of ethically based clinical trials [2]. Critically important is the use of tools that are justified both ethically and scientific researches [11, 12].

*Bases for used methodology.* Therapy prescriptions should not be based on hypotheses, but on clinical studies that confirm the effectiveness of such therapy. Hypotheses, however, may be the basis for a planned clinical trial [13]. Therefore, it seems reasonable to apply simulation modeling of coronaviral disease course and exposure to pharmacological drugs.

The methods of information technologies and mathematical modeling complement those of experimental biology and medicine. Modern diagnostic methods, whatever perfect

they may be, give only a “slice” of current organism state. Therefore, the mathematical modeling of organism functional systems and an organism as a whole became widespread in the last third of the last century, allowing to simulate various processes taking place in the organism and to study these processes at the level inaccessible to the modern methodical diagnosis level, for example, to simulate extreme organism disturbances and forecast the functional state of organs and systems with this disturbance.

Mathematic model of functional respiratory system, developed by the united efforts of the scientists from Glushkov Institute of Cybernetics and Bogomoletz Institute of Physiology both of the National Academy of Sciences of Ukraine was based exactly on these principles.

The purpose of the work was to create integrated mathematical model to simulate the course of the disease caused by SARS-CoV-2 virus and pharmacological correction of complications — organism hypoxic states.

### Mathematical models of respiration and blood circulation systems

Many mathematical models of various functional systems and organism as a whole exist nowadays. Let's observe the models related to the respiratory and blood circulatory systems because of several reasons. First, according to the current information, exactly these systems are the most affected by the SARS-CoV-2 virus [14–27]. Secondly, in the theory of adaptation developed by Meyerson, exactly these systems responded most noticeably to changes of living conditions [28, 29]. Thirdly, in a number of publications there were shown that if we consider the human organism from the point of view of reliability theory, and assume it as a “chain with a weak link”, then such “weak links” are exactly the respiratory and blood circulatory systems [30–37].

First of all, Gray model should be highlighted, in which the respiratory system was presented as a feedback system and thus the background for studying the relationships between alveolar ventilation  $V$  and oxygen pressures  $pO_2$ , carbon dioxide  $pCO_2$  and the arterial blood acidity  $pH$  was laid [38].

The next qualitatively important step was the model of Grodins, who suggested that the respiratory system should be considered as a dynamic system, which made it possible to use the appropriate mathematical apparatus [39, 40]. The ventilation dynamics was studied

when the concentration of carbon dioxide in respiratory system changed. Therewith elements of system analysis were used. The control and controlled systems responsible for process of gas exchange were given up, tissue reservoirs of an organism in which oxygen was consumed and carbon dioxide was released were subdivided. Two reservoirs were identified as “brain” and “non-brain”. The first reservoir included vitally important organs, the second one — peripheral organs and tissues. Grodins derived the differential equations describing the dynamics of partial pressures and tensions of respiratory gases in the lungs, blood and tissues, basing on the principles of material balance and continuity of the flow [39, 40]. A significant disadvantage of the model was the assumption that during inspiration, a constant  $pCO_2$  was maintained in the respiratory mixture, alveoli and blood.

**Mathematical models of respiratory and blood circulatory systems: their use for the solution of practical and theoretical problems in medicine and physiology**

Further development of Grodins model was a model of mass transfer and mass exchange of respiratory gases in human body and dolphin, proposed by Kolchinskaya and Misyura [41]. The model considers the process of mass transfer and mass exchange of respiratory gases through the alveolar-capillary and capillar-tissue membranes, taking into account their structural and functional peculiarities. This approach enabled to study gases transportation in human body during respiratory cycle: inspiration, expiration and pause, taking into account the biophysical and biochemical characteristics of the processes. Besides, tissue reservoirs were differentiated in the model, tissues of brain, heart, liver, kidneys, skeletal muscles, and etc. were defined. This made it possible to elaborate the models of gases saturation and to study the process of hypoxia development in them [41]. The proposed model contained equations for determining of alveolar ventilation and systemic blood flow obtained on the basis of experimental data. However in order to calculate oxygen and carbon dioxide regimes of human organism under changes in living conditions, it was required the data that were impossible to obtain at the current methodological level of bioexperiment. Therefore, it is quite problematic to use such type of models for the cases upon changing the

levels of energy consumption, environmental conditions without solving the problem concerning control of respiratory system function.

In addition, blood circulatory system, contrary to respiratory one, is multifunctional, and this causes certain difficulties linked with determination of optimality criterion. Consequently, the concept of organism's oxygen regimes regulation formulated by Kolchinskaya and Lauer was an actual one [42]. According to this concept, the regulation in organism is carried out by one complex system that coordinates joint functioning of various mechanisms and subordinates this system to its main task — to maintain optimal oxygen parameters along the oxygen pathes in organism. Herewith, the delivery speed should match the oxygen demand in tissues. In accordance with this concept, mathematical models should consider the united action of the systems of external respiration, blood circulation, and tissue respiration, aimed on the providing of tissues demand in oxygen.

There are numerous other mathematical models [43–52]. Let's observe exactly the models developed by Onopchuk and representatives of his scientific school [37, 53–59]. Basing on above-described approach, few mathematical models of heat transfer and heat exchange [60–62], immune system [63–65], system of energy supply [66] and erythropoiesis [67, 68] were developed.

These models were used to solve a number of practical and theoretical problems in medicine and physiology. Namely, the theoretical problems linked with investigations of cerebral blood circulatory tensions in operators of continuous interaction system were solved [69–74], compromise resolution of conflict situations in the problem of optimal control in decisions making in difficult situations was studied [37, 75–77], the role of hypoxia, hypercapnia and hypometabolism during adaptation of the respiratory system to intensive muscular activity and stay in conditions of hypoxic hypoxia were investigated [78–82], mathematical models of short-term, medium-term and long-term adaptation of the respiratory system to extreme environmental influences were developed [35, 37, 83, 84], parameters of self-organization of the rescue command members breathing system during short-term and medium-term adaptation to hypoxic hypoxia were studied [35, 82], the tasks of modeling of the hypoxic and hypercapnic stages of training athletes were considered [85, 86], dependence of parameters of functional self-organization for high qualification

women-athletes on the hormonal status of their organisms were studied [87–89], algorithm for predicting of fatigue development in highly skilled athletes with refined muscular activity was constructed [90, 91], mathematic models for the development of hypoxia at coronary heart disease were developed [92–97], algorithm for the selection of data models and algorithms for their processing to build an integrated estimation of the reliability and performance of athletes was proposed [98–101]. Separately, it is necessary to highlight the use of these models in sports of the highest achievements, for the sportsmen specializing in cyclic sports [102], martial arts [103–107], alpinism [108], their practical application in research at the Elbrus Medical and Biological Station of Bogomoletz Institute of Physiology of the National Academy of Sciences of Ukraine [109–121], for solution of a broad range of problems connected with the examination of operators of continuously interacting systems and flying personnel.

Separately, it is necessary to write about the works [122–124] associated with the development of software for the improving of the tools and methods for operational data mining, processing and analysis of functional diagnostic data, and the person's stay in hyperbaric environment [125, 126].

There is also a number of works devoted to the research and identification of organism reserves under the extreme disturbances [127–132] and optimization of the recovery and rehabilitation processes after the extreme loads on an organism [133,134], thermoregulation processes under the extreme influences [116].

Therefore, the idea to apply such models for new class of problems related to studying

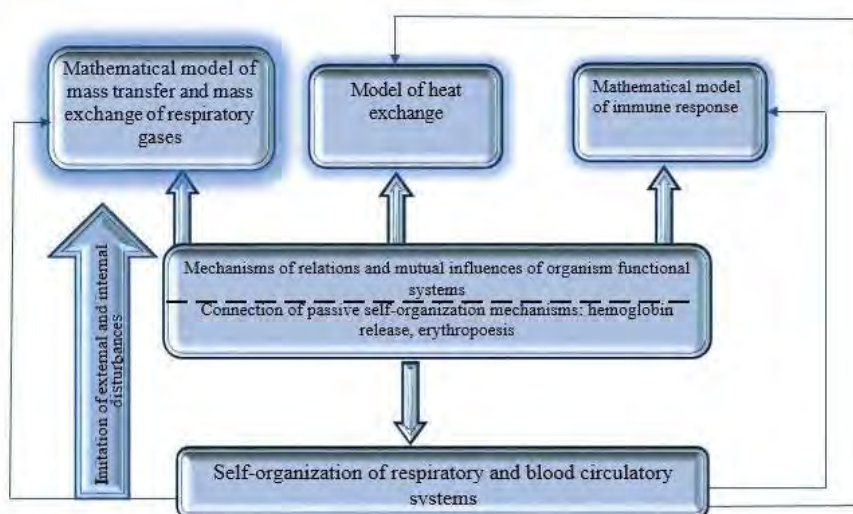
and treatment of infectious organism lesions infected with SARS-CoV-2 seems quite reasonable and appropriate.

### **Integrated model of the functional system of respiration, blood circulation, heat transfer, and immune response**

To simulate the hypoxic state caused by SARS-CoV-2 virus we proposed to use integrated mathematical model of the functional respiratory and blood circulatory system, thermoregulation, and immune response to predict the course of viral disease [37, 54, 55, 57, 60–65].

When studying the organism adaptation to one or another disturbances, including infectious disease, it is advisable to take into consideration the possibility of participation of intersystem mechanisms in process of organism state stabilizing, taking into account both intra-systemic and intersystemic conflict situations. In response to the environment disturbing influence (external or internal), all organism functional systems react against it to some extent, trying to stabilize the organism state, despite the contradictions between goals and interests. The structural scheme of complex mathematical model for investigation of the main functional systems (respiration, blood circulation, heat transfer, immune), their pharmacological correction as well as mechanisms of their interaction and interconnection during the life activities in extreme conditions of the external and internal environment was shown on Fig. 1.

Let's give a description of the models of individual functional systems. Briefly,



*Fig. 1. Integrated model of the functional system of respiration, blood circulation, heat transfer, and immune response*



the mathematical model of the functional respiratory system could be represented as follows. Mathematical model of respiratory and blood circulatory system is a controlled dynamic system, the phase state of which is characterized by partial pressures and tensions of respiratory gases in each element of the system.

The controlled part of the model is based on differential equations describing changes in average partial pressures of respiratory gases in each part of respiratory cycle — during inspiration, expiration and pause. Briefly, the model can be submitted as follows:

$$\frac{dp_i O_2}{d\tau} = \varphi(p_i O_2, p_i CO_2, \eta_i, \dot{V}, Q, Q_i, G_i O_2, q_i O_2) \quad (1)$$

$$\frac{dp_i CO_2}{d\tau} = \psi(p_i O_2, p_i CO_2, \eta_i, \dot{V}, Q, Q_i, G_i CO_2, q_i CO_2) \quad (2)$$

where the functions  $\varphi$  and  $\psi$  are described in detail in [54, 55],  $V$  is ventilation,  $\eta$  is a degree of hemoglobin saturation with oxygen,  $Q$  is volumetric velocity of systemic and  $Q_{t_i}$  — local blood flows,  $q_{t_i} O_2$  is oxygen consumption rate by  $i$ -th tissue reservoir,  $q_{t_i} CO_2$  is the rate of carbon dioxide release in  $i$ -th tissue reservoir. The velocities  $G_{t_i} O_2$  of oxygen flows from the blood into the tissue and  $G_{t_i} CO_2$  of carbon dioxide from the tissue into the blood are determined by the ratio:

$$G_{t_i} = D_{t_i} S_{t_i} (p_{ct_i} - p_{t_i}) \quad (3)$$

where  $D_{t_i}$  are gas permeability coefficients through the airhematic barrier,  $S_{t_i}$  is gas exchange surface area.

In this model, respiratory, cardiac and vascular smooth muscles are the active mechanisms of self-regulation. Accordingly  $V, Q, Q_{t_i}, i = 1, m$  are the control parameters in the dynamic system, which are determined as a result of solving the task of optimal output of the disturbed dynamic system into a stable equilibrium state characterized by the following retios:

$$G_{t_i} O_2 - q_{t_i} O_2 = 0, \quad i = \overline{1, m} \quad (4)$$

$$G_{t_i} CO_2 + q_{t_i} CO_2 = 0, \quad i = \overline{1, m} \quad (5)$$

The optimal values are those that provide a minimum of the functional:

$$I = \int_{t_0}^T \left( \rho_1 \sum_{t_i} \lambda_{t_i} (G_{t_i} O_2 - q_{t_i} O_2)^2 + \rho_2 \sum_{t_i} \lambda_{t_i} (G_{t_i} CO_2 + q_{t_i} CO_2)^2 \right) dt \quad (6)$$

under the restrictions:

$$\dot{V}^{\min} \leq \dot{V} \leq \dot{V}^{\max}, \quad Q^{\min} \leq Q \leq Q^{\max}, \quad Q_{t_i}^{\min} \leq Q_{t_i} \leq Q_{t_i}^{\max}, \quad \sum_{t_i} Q_{t_i} = Q \quad (7)$$

In (7)  $\rho_1, \rho_2$  are organism sensitivity coefficients to the oxygen deficiency and carbon dioxide excess,  $\lambda_{t_i}$  characterize functionally the morphological features of tissue region.

The dynamics of infectious lesion of organism was given by Marchuk as a system of ordinary nonlinear differential equations with delay [135]. Let's consider one of the equations of this system:

$$\frac{dm}{d\tau} = \sigma v(1-m) - \mu_m \quad (8)$$

where  $m(\tau)$  is relative characteristics of an affected organ. If  $M$  is characteristics of healthy organ (mass or area), and  $M'$  is corresponding characteristic of the healthy part of affected organ, then

$$m = 1 - \frac{M'}{M} \quad (9)$$

is a relative characteristic of lesion of an organ-target. The factor  $(1 - m)$  in (8) determines the effect of antigens on unaffected part of an organ-target.

Decrease in this characteristic occur due to the regenerative activity of an organism with  $\mu_m$  coefficient characterizing the rate of mass recovery of the affected organ.

The pathological state of an organism that developed due to the infectious lesion can be considered as disturbance during modeling of blood circulatory system. Then  $\sigma$  and  $\mu_m$  in (8) are the functions depended on  $Q_{t_i}$ . When considering joint modeling of respiratory, circulatory and immune systems and their regulation, it is necessary to add the term

$$\rho_{\eta_i} f_i^2(m(\tau), V(\tau)) \quad (10)$$

to the quality criterion of regulation (6) into the integration element, where  $\rho_{\eta_i}$  is a coefficient characterizing the influence degree of the simulated disease type on the level of gas homeostasis. The function  $f_i(m, V)$  determines the damage degree of target-organ at current moment. At control points, this function was taken as:

$$f_i(m, V) = a_i m + b_i v \quad (11)$$

It could be assumed that the flow of energy processes in the tissues of an organ-target is supplied only due to its unaffected part. Then the mass of metabolizing part of the organ will

be determined:

$$v_{t_i}(\tau) = v_{t_i}^0(1 - m(\tau)), \quad (12)$$

where  $v_{t_i}^0$  is a total mass (volume) of tissues of healthy organ.

In case of infectious disease, it is natural to assume a reaction of thermoregulatory system. Let's complete our model of the dynamics of the course of infectious disease by introducing the variable  $T$  (the temperature of internal sphere of organism [136, 137]) in the equation below:

$$\frac{dT_k}{dt} = K_T(Fv - (Fv)^*)\chi(Fv - (Fv)^*) - \mu_T(T_k - T_k^*), \quad (13)$$

where  $K_T$ ,  $\mu_T$  are coefficients,  $Fv$  is concentration of  $Fv$  complexes,  $(Fv)^*$  is maximal permissible concentration of complexes,  $T_{t_k}^*$  is normal temperature of core of organism,  $\chi$  is Heaviside function. In this case, it was natural to put the coefficients in model (8)–(12) in the form of functions depending on  $T_{t_k}$ :

$$\bar{\beta}(T_k) = \frac{\bar{\beta}(T_k^*)}{1 + \alpha_{T_k}(T_k - T_k^*)}, \quad (14)$$

$$\bar{\alpha}_{T_k} = \bar{\alpha}(T_k^*)[1 + b_{T_k}(T_k - T_k^*)], \quad (15)$$

where  $\bar{\beta}(T_k^*) = \bar{\beta}$ ,  $\bar{\alpha}(T_k^*) = \bar{\alpha}$ ,  $\alpha_{T_k}$ ,  $b_{T_k}$  are coefficients.

It is natural to assume that at the initial stage of disease, the passive mechanisms of self-regulation such as erythropoiesis, release of hemoglobin and mioglobin into blood were involved. An increase of the content of red blood cells and the content of hemoglobin in them is powerful regulatory mechanism for maintaining of organism stable state in conditions that lead to oxygen deficiency under the various disturbances. In [67] the linear dependences of erythropoetin (EPO),  $Ht$  and  $Hb$  were obtained and than they were introduced into the mathematical model of functional respiratory and blood circulatory system to enhance the regulation of respiratory system main function in hypoxia.

Further, due to the fact that severe hypoxia develops in organism as a result of lung damage, the injection of antihypoxants into the organism is advisable in order to study the possible ways of organism state relief in case of hypoxia. The integrated model described above for this case has to be supplemented by the equations of transport of pharmacological preparations in organism in forms, suggested

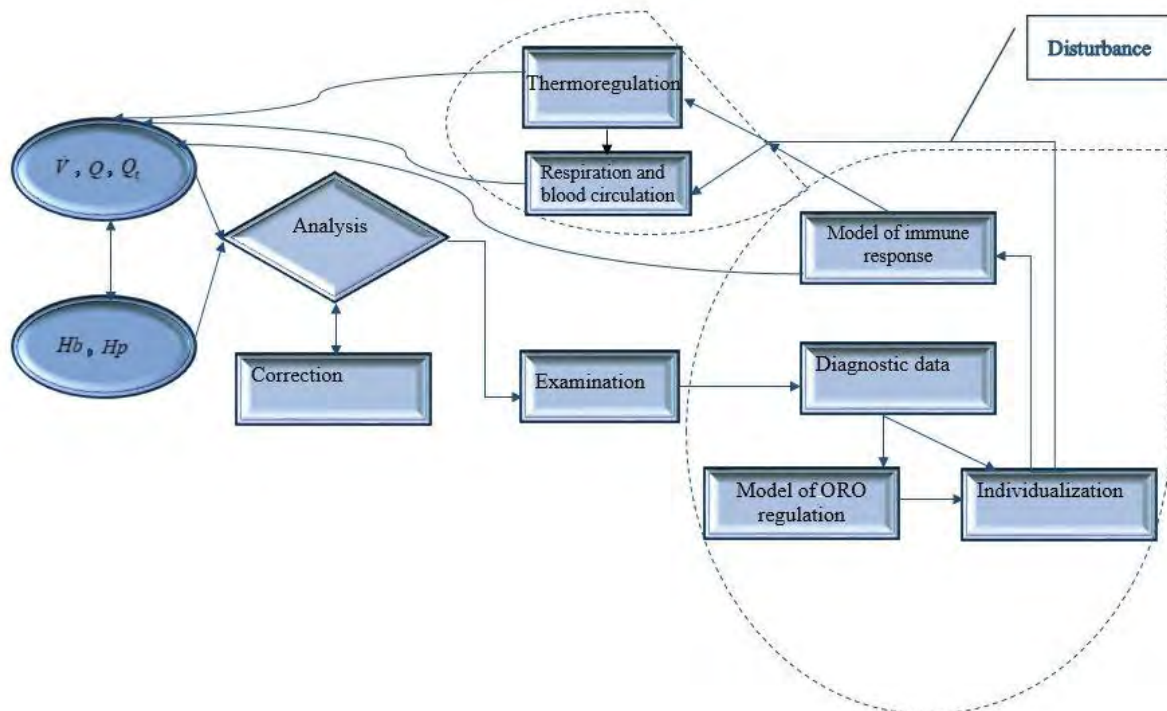
previously [107, 118, 138]. The algorithm for the application of this approach is given in Fig. 2.

Our developed mathematical model of pharmacological correction of hypoxic states clarifies the role of pharmacological preparation use for prevention of hypoxic states development in organism (for organism state perfection). It was assumed that the withdrawal of antihypoxant  $f$  from the organism is carried out through the kidneys. It was assumed as well that we use pharmacological preparations that improve oxygen permeability through the capillary tissue membranes of blood vessels. According to this scheme it was assumed that the most effective was intravenous administration of antihypoxant, although the model enabled to simulate as well as respiratory, oral and intramuscular way of antihypoxants administration.

### Procedure for the work with the model

1. Patient examination is carried out.
2. The data obtained from the survey are the source for calculation of organism oxygen regimes [121, 122].
3. The data obtained during patient examination and some data obtained as a result of calculation of organism oxygen regimes were taken as input source data in the models of functional respiratory system, blood circulatory system and thermoregulation. In such a way the models individualization was fulfilled.
4. Further, using the model of immune response, the effect of virus is simulated; with the interaction and interinfluence of the models, the partial pressures and tensions of respiratory gases in all parts of respiratory system, alveolar ventilation and systemic blood flows are calculated.
5. The next step is to simulate the effects of pharmacological preparations and, consequently, the values of the same indicators have to be calculated again.
6. The obtained data are analyzed and further, in case of unsatisfactory result, another effect of antihypoxant is simulated, or if the obtained indicators are acceptable, then this scheme of pharmacological preparation use is chosen.

Thus in this publication, the results of development of comprehensive integrated mathematical model for simulation of the course of disease caused by SARS-CoV-2 were suggested. It could be used



**Fig. 2. Scheme of mathematical model for simulating the course of viral disease and its pharmacological correction:**  $Hb, BH$  — concentrations of hemoglobin and buffer bases in blood;  $Q$  — volumetric velocity of systemic blood flow;  $Q_{ti}$  — volumetric velocity of local blood flows;  $ORO$  — oxygen regimes of organism;  $v$  — alveolar ventilation (air volume that pass through alveolar space during 1 min)

for pharmacological correction of hypoxic states that occur with the complication of disease course as well. The bases for the used methodology were observed as well as mathematical models of respiration and blood circulation systems. The information about the developed models of respiratory and blood circulatory systems and their use for the solution of practical and theoretical problems in medicine and physiology were suggested. For simulation of hypoxic state caused by SARS-CoV-2, we proposed to use the integrated mathematical model of functional respiratory and blood circulatory systems, thermoregulation, and immune response one to forecast the course of viral disease. The structural scheme of complex mathematical model for the investigations of main functional systems (respiration, blood circulation, heat transfer, and immune response), their pharmacological correction as well as mechanisms of their interaction and interconnection during the life activities in extreme conditions of the external and internal environment was demonstrated. In the result, the complex of information support for imitation of viral disease course as well as for its pharmacological correction caused by the organism hypoxic states were developed.

For today, this mathematical integrated model has theoretical significance only. It is based on the information about the clinically registered manifestations of coronaviral (SARS-CoV-2) disease available in the public domain. Therefore, this model requires further perfection. In particular, it seems necessary to clarify some characteristics of respiratory gases transport through the alveolar-capillary membrane, peculiarities of gas exchange in the alveolar space, which cause the decrease of blood oxygenation. These are the problems that need to be solved in close collaboration with the professionals in medicine. At the same time, the imitation on this model the development of infectious disease and associated hypoxic state is one of the possible and quite effective tool for solving the tasks associated with the support of patients in acute hypoxic respiratory and heart failure caused by the complications of viral (SARS-CoV-2) disease.

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## REFERENCES

1. Novel coronavirus (2019-nCoV). *WHO/Europe*. World Health Organization (9 March 2020). Available at [http://www.euro.who.int/en/health-topics/health-emergencies/novel-coronavirus-2019-ncov\\_old](http://www.euro.who.int/en/health-topics/health-emergencies/novel-coronavirus-2019-ncov_old)
2. *Nicholas J. Beeching, Tom E. Fletcher, Robert Fowler*. COVID-19. *BMJ Best Practices*. BMJ Publishing Group (17 February 2020).
3. *David L. Heymann, Nahoko Shindo*. COVID-19: what is next for public health? *The Lancet*. Elsevier, 2020.13 February. ISSN 1474-547X 0140-6736, 1474-547X. [https://doi.org/10.1016/S0140-6736\(20\)30374-3](https://doi.org/10.1016/S0140-6736(20)30374-3)
4. Prevention, diagnosis and treatment of new coronavirus infection (COVID-19). Temporal methodical recommendations. *Health Ministry of Russia*. (March 3, 2020). [https://static-0.rosminzdrav.ru/system/attachments/attaches/000/049/629/original/MP\\_COVID-19\\_03.03.2020\\_\(In\\_Russian\).pdf?sfvrsn=8b671ce5\\_2](https://static-0.rosminzdrav.ru/system/attachments/attaches/000/049/629/original/MP_COVID-19_03.03.2020_(In_Russian).pdf?sfvrsn=8b671ce5_2)
5. Available at [https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200128-sitrep-8-ncov-cleared.pdf?sfvrsn=8b671ce5\\_2](https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200128-sitrep-8-ncov-cleared.pdf?sfvrsn=8b671ce5_2)
6. Available at [https://emcrit.org/ibcc/covid19/CDC\\_Novel\\_Coronavirus\\_2019\\_Situation\\_Summary](https://emcrit.org/ibcc/covid19/CDC_Novel_Coronavirus_2019_Situation_Summary).
7. WHO recommendations to the public regarding the spread of the new coronavirus (2019-nCoV): myths and misconceptions. Available at [https://ru.wikipedia.org/wiki/Coronaviral\\_infection\\_COVID\\_19\\_\(In\\_Russian\)](https://ru.wikipedia.org/wiki/Coronaviral_infection_COVID_19_(In_Russian)).
8. WHO recommendations to the public regarding the spread of the new coronavirus (2019-nCoV): myths and misconceptions COVID-19. Available at [https://www.who.int/ru/emergencies/diseases/novel-coronavirus-2019/advice-for-public/q-a-c\\_\(In\\_Russian\)](https://www.who.int/ru/emergencies/diseases/novel-coronavirus-2019/advice-for-public/q-a-c_(In_Russian)).
9. How to Protect Yourself & Others. Available at [https://www.cdc.gov/coronavirus/2019-ncov/prevent-getting-sick/prevention.html?CDC\\_AA\\_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fprepare%2Fprevention.html](https://www.cdc.gov/coronavirus/2019-ncov/prevent-getting-sick/prevention.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fprepare%2Fprevention.html)
10. *Srinivas Murthy, Charles D. Gomersall, Robert A. Fowler*. Care for Critically Ill Patients With COVID-19. *Jama*. 2020, 11 March. <https://doi.org/10.1001/jama.2020.3633>
11. *Anthony S. Fauci, H. Clifford Lane, Robert R. Redfield*. Covid-19 — Navigating the Uncharted. *New Engl. J. Med*. 2020, 28 February. <https://doi.org/10.1056/NEJMe2002387>
12. *Yonghong Xiao, Mili Estee Torok*. Taking the right measures to control COVID-19. *The Lancet Infectious Diseases*. Elsevier. 2020, 5 March. [https://doi.org/10.1016/S1473-3099\(20\)30152-3](https://doi.org/10.1016/S1473-3099(20)30152-3)
13. *Rebrova O. Yu., Vlasov V. V., Baschinsky S. E., Aksyonov V. A.* TWIMC: SDMX comment on coronavirus infection. *OSDM* (March 22, 2020). 2020. <http://osdm.org/blog/2020/03/22/twimc-komentarij-osdm-o-koronavirusnoj-infekcii/>
14. *Xu X. Chen P., Wang J.* Evolution of the novel coronavirus from the ongoing Wuhan outbreak and modeling of its spike protein for risk of human transmission: *Science China Life Sciences*. <https://doi.org/10.1007/s11427-020-1637-5>. PMID 32009228.
15. *Letko Michael, Munster Vincent*. Functional assessment of cell entry and receptor usage for lineage B  $\beta$ -coronaviruses, including 2019-nCoV. *BioRxiv : journal*. 2020, 22 January, P. 2020.01.22.915660. <https://doi.org/10.1101/2020.01.22.915660>
16. *Zhou Peng, Shi Zheng-Li*. Discovery of a novel coronavirus associated with the recent pneumonia outbreak in humans and its potential bat origin. *BioRxiv: journal*. 2020, P. 2020.01.22.914952. <https://doi.org/10.1101/2020.01.22.914952>
17. *Gralinski L. E., Menachery V. D.* Return of the Coronavirus: 2019-nCoV. *Viruses*. 2020, 12 (2), 135. <https://doi.org/10.3390/v12020135>. PMID 31991541.
18. European Centre for Disease Prevention and Control, Novel coronavirus (2019-nCoV) infections, p. 8.
19. *Ke Wang, Wei Chen, Yu-Sen Zhou, Jian-Qi Lian, Zheng Zhang, Peng Du, Li Gong, Yang Zhang, Hong-Yong Cui, Jie-Jie Geng, Bin Wang, Xiu-Xuan Sun, Chun-Fu Wang, Xu Yang, Peng Lin, Yong-Qiang Deng, Ding Wei, Xiang-Min Yang, Yu-Meng Zhu, Kui Zhang, Zhao-Hui Zheng, Jin-Lin Miao, Ting Guo, Ying Shi, Jun Zhang, Ling Fu, Qing-Yi Wang, Huijie Bian, Ping Zhu, Zhi-Nan Chen*. SARS-CoV-2 invades host cells via a novel route: CD147-spike protein. *BioRxiv: journal*. <https://doi.org/10.1101/2020.03.14.988345>
20. *Zhonghua Liu Xing Bing Xue Za Zhi*. Novel Coronavirus Pneumonia Emergency Response Epidemiology Team. [The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19). (In China). 2020, 41 (2), 145–151. <https://doi.org/10.3760/cma.j.isn.0254-6450.2020.02.003>. PMID 32064853.
21. *Li Q., Guan X., Wu P., Wang X., Zhou L., Tong Y., Ren R., Leung K. S., Lau E. H., Wong J. Y., Xing X., Xiang N., Wu Y., Li C., Chen Q., Li D., Liu T., Zhao J., Li M., Tu W., Chen C., Jin L., Yang R., Wang Q., Zhou S., Wang R., Liu H., Luo Y., Liu Y., Shao G., Li H., Tao Z., Yang Y., Deng Z., Liu B., Ma Z., Zhang Y., Shi G., Lam T. T., Wu J. T., Gao G. F., Cowling B. J., Yang B., Leung G. M., Feng Z.* Early



- Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia. *The New England Journal of Medicine*. 2020. January. <https://doi.org/10.1056/NEJMoa2001316>. PMID 31995857.
22. Charles Calisher, Dennis Carroll, Rita Colwell, Ronald B. Corley, Peter Daszak. Statement in support of the scientists, public health professionals, and medical professionals of China combatting COVID-19. *The Lancet*. Correspondence. Elsevier. 2020, 18 February. [https://doi.org/10.1016/S0140-6736\(20\)30418-9](https://doi.org/10.1016/S0140-6736(20)30418-9)
  23. Zhao Shi, Ran Jinjun, Musa Salihu Sabiu, Yang Guangpu, Lou Yijun, Gao Daozhou, Yang Lin, He Daihai. Preliminary estimation of the basic reproduction number of novel coronavirus. *BioRxiv*. 2019, 24 January.
  24. Qun Li, Xuhua Guan, Peng Wu, Xiaoye Wang, Lei Zhou. Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia. *New England Journal of Medicine*. 2020-01-29. [https://doi.org/10.1016/S0140-6736\(20\)30418-9](https://doi.org/10.1016/S0140-6736(20)30418-9) 10.1056/NEJMoa2001316
  25. Ji W., Wang W., Zhao X. Homologous recombination within the spike glycoprotein of the newly identified coronavirus may boost cross-species transmission from snake to human. *Journal of Medical Virology*. Hoboken, New Jersey: Wiley-Blackwell. 2020, January, P. 1–29. ISSN1096-9071. <https://doi.org/10.1002/jmv.25682>. PMID 31967321
  26. Neeltje van Doremalen, Trenton Bushmaker, Dylan H. Morris, Myndi G. Holbrook, Amandine Gamble. Aerosol and Surface Stability of SARS-CoV-2 as Compared with SARS-CoV-1. *New England Journal of Medicine*. 2020-03-17, P. NEJMc2004973. <https://doi.org/10.1056/NEJMc2004973>
  27. Peng Zhou, Xing-Lou Yang, Xian-Guang Wang, Ben Hu, Lei Zhang, Wei Zhang, Hao-Rui Si, Yan Zhu, Bei Li, Chao-Lin Huang, Hui-Dong Chen, Jing Chen, Yun Luo, Hua Guo, Ren-Di Jiang, Mei-Qin Liu, Ying Chen, Xu-Rui Shen, Xi Wang, Xiao-Shuang Zheng, Kai Zhao, Quan-Jiao Chen, Fei Deng, Lin-Lin Liu, Bing Yan, Fa-Xian Zhan, Yan-Yi Wang, Gengfu Xiao, Zheng-Li Shi. Discovery of a novel coronavirus associated with the recent pneumonia outbreak in humans and its potential bat origin *BioRxiv*. 2020, January, 18 p. <https://doi.org/10.1101/2020.01.22.914952>
  28. Meerson F. Z. General mechanism of adaptation and role of stress-reaction in it, main stages of the processes. *Moskva: Nauka*. 1986, P.77–123. (In Russian).
  29. Meerson F. Z., Pshennikova M. G. Adaptation to stressed situations and physical loadings. *Moskva: Medicina*. 1988, 256 p. (In Russian).
  30. Onopchuk Yu. N., Beloshitsky P. V., Aralova N. I. To the question of the reliability of functional organism systems. *Kibernetika i vychislitelnaâ tehnika*. 1999, Is. 122, P. 72–82. (In Russian).
  31. Beloshitsky P. V., Onopchuk Yu. M., Aralova N. I. Mathematical methods for the investigation of the problem of organism functioning reliability at extreme high mountains conditions. *Physiol. J.* 2003, 49 (3), 47–54. (In Russian).
  32. Beloshitsky P. V., Onopchuk Yu. N., Aralova N. I. Mathematical methods for investigating the reliability of organisms functioning under the extreme conditions of high mountains. *High Altitude medicine and biolog.* 2002, 3 (1), 129.
  33. Beloshitsky P. V., Onopchuk Yu. N., Aralova N. I. Investigation the reability of the functioning of organisms systems under high-altitude conditions. Mathematical modelling. *Scientific Highlights 1999–2002, International Centre for Astronomical, Medical and Ecological Research. Kyiv*. 2002.
  34. Onopchuk Yu., Beloshitskiy P., Aralova N. Stability, adaptation and reliability of an organism's functional systems under hypoxia. "The 3<sup>rd</sup> World Congress on Mountain Medicine and High Altitude Physiology and the 18<sup>th</sup> Japanese Symposium on Mounain Medicine, May 20<sup>th</sup>–24<sup>th</sup>". 1998. *Matsumoto, Japan*.
  35. Aralova N. I. Mathematical model of the mechanism short- and medium-functional adaptation of breath of persons work in extreme conditions high. *Kibernetika i vychislitelnaâ tehnika*. 2015, V. 182, P. 15 25.
  36. Aralova N. I., Klyuchko O. M., Mashkin V. I., Mashkina I. V. Software for the reliability investigation of operator professional activity for "human-machine" systems. *Electronics and control systems*. 2017, V. 1, P. 107–115. <https://doi.org/10.18372/1990-5548.51.11712>
  37. Aralova N. I. Mathematical models of functional respiratory system for solving the applied problems in occupational medicine and sports. *Saarbrücken: LAP LAMBERT Academic Publishing GmbH&Co, KG*. 2019, 368 p. (In Russian). ISBN 978-613-4-97998-6
  38. Gray J. S. The multiple factor theory of respiratory regulation. *Science*. 1946, V. 103, P. 739–743.
  39. Grodins F. S., Buell J., Bart A. J. Mathematical analysis and digital simulation tje respiratory control system. *J. Appl. Physiol.* 1967, 22 (2), 272.
  40. Grodinz F. Theory of regulation and biological systems. *Moskva: Mir*. 1966, 315 p. (In Russian).

41. Kolchinskaya A. Z., Misyura A. G., Mankovskaya I. N. Respiration and oxygen regimes of dolphins. *Kyiv: Nauk. dumka.* 1980, 332 p. (In Russian).
42. Lauer N. B., Kolchinskaya A. Z. About the oxygen organism regime Oxygen organism regime and its regulation. *Kyiv: Nauk. dumka.* 1966, P. 157–200. (In Russian).
43. Marchuk G. I. Mathematic modeling in the problem of environment. *Moskva: Nauka.* 1982, 320 p. (In Russian).
44. Dickinson C. J. A computer model of human respiration. *Lancaster: Medical and Technical Publishing.* 1977, 294 p.
45. Amosov N. M., Paletz B. L., Agapov B. T. Theoretical investigations of physiological systems. *Kyiv: Nauk. dumka.* 1977, 246 p. (In Russian).
46. Amosov N. M., Paletz B. L., Agapov B. T., Ermakova I. I., Liabah E. G., Theoretical investigations of physiological systems. *Kyiv: Nauk. dumka.* 1977, 246 p. (In Russian).
47. Marchuk G. I. Mathematic models in immunology. *Moskva: Nauka.* 1991, 304 p. (In Russian).
48. Novoseltsev V. N. Theory of control and biosystems. *Moskva: Nauka.* 1978, 319 p. (In Russian).
49. Amosov N. M. Regulation of vital functions and cybernetics. *Kyiv: Nauk. dumka.* 1998, 366 p. (In Russian).
50. Antononov Yu. G. Modeling of biological systems. *Kyiv: Nauk. dumka.* 260 p. (In Russian).
51. Secondary tissue hypoxia. Ed. Kolchinskaya A. Z. *Kyiv: Nauk. dumka.* 1983, 253 p. (In Russian).
52. Shumakov V. N., Novoseltsev V. N., Sacharov V. P., Shtengold. Modeling of organism physiological systems. *Moskva: Medicine.* 1971, 352 p. (In Russian).
53. Onopchuk Yu. N. Controlled models of gases dynamics in organism and their numerical analysis. *Theases for the obtaining the scientific degree of doctor of phys.-mat. sciences.* *Kyiv.* 1984, 45 p. (In Russian).
54. Onopchuk Yu. N. Homeostasis of functional respiratory system as a result of intersystem and system-medium informational interaction. *Bioecomedicine. Uniform information space.* Ed. by V. I. Gritsenko. *Kyiv.* 2001, P. 59–84. (In Russian).
55. Onopchuk Yu. N. Homeostasis of the functional circulatory system as a result of intersystem and system-medium informational interaction. *Bioecomedicine. Uniform information space.* Ed. by V. I. Gritsenko. *Kyiv.* 2001, P. 85–104. (In Russian).
56. Polynkevich K. B., Onopchuk Yu. N. Conflict situations at regulating of the main function of organism respiratory system and mathematical models of their resolution. *Cybernetics.* 1986, V. 3, P. 100–104. (In Russian).
57. Aralova N. I., Aralova A. A. Mathematical models of conflict controlled processes under functional self- organization of the respiratory system. *Cyb. comp. eng.* 2019, 3 (197), 65–79. <https://doi.org/10.15407/kvt197.03.065>
58. Galchyna N. I., Onopchuk Iu. N., Portnichenko V. I., Siemchyk T. A. Game models for the control of the main body functional systems and their analysis. *Cybernetics and system analysis.* 2014, 50 (1), 77–92.
59. Galchyna N. I., Onopchuk Iu. N., Portnichenko V. I., Siemchyk T. A. Game models for the control of the main body functional systems and their analysis. *Cybernetics and system analysis.* 2014, 50 (2), 89–98.
60. Onopchuk Y. N., Loziychuk N. G. Mathematical model and organism systems for thermoregulation and their analysis. *Cybernetic and system analysis.* 1995, N 4, P. 152–160. (In Russian).
61. Loziychuk N. G., Marchenko D. I., Onopchuk D. I. About one model of heat exchange in organism and its quantitative and qualitative homeostasis. *Kibernetika i vyčislitelnaâ tehnika.* 1987, N 74, P. 80–82. (In Russian).
62. Loziychuk N. G. Mathematical model of control of the level of temperature homeostasis. *Kibernetika i vyčislitelnaâ tehnika.* 1989, N 82, P. 77–80. (In Russian).
63. Semchyk T. A. Mathematical model of the hypoxia course process under infectious diseases, the ischemic heart diseases and their analysis. *Theases for the obtaining the scientific degree of Candidate of Technical Sciences on speciality 01.05.02 — mathematical modeling and computational methods.* V. M. Glushkov Institute of Cybernetics of the National Academy of Sciences of Ukraine. *Kyiv.* 2007, 20 p.
64. Semchyk T. A. The mathematical model of immune response on infectious damage to an organism and mechanisms of its interaction with models of respiration, blood circulation and heat exchange. *Theory of optimal solution.* 2018, V. 17, P. 92–98.
65. Aralova N. I., Shakhlina L. Ya. G., Futornyi S. M. Mathematical model of the immune system of hight qualification athlete. *Journal of Automation and Information Sciences.* 2019, V. 2, P. 130–142.
66. Galchina N. I. Mathematical models of energy resource assessment in strenuous activity and post-activity recovery. *Cybernetics and system analysis.* 2014, 50 (2), 940–944.
67. Garaschenko F. G., Lanovenko I. I., Grabova N. I. About one mechanism of autoregulation of process of breath in the

- organism and is mathematical model. *Theory of optimal solution*. 2008, V. 7, P. 139–145.
68. Galchyna N. I., Korniyush I. I., Semchyk T. A. Mathematical models for complex assessment of the functional condition of the human body in extreme conditions. *Theory of optimal solutions*. 2019, V. 18, P. 13–18.
  69. Aralova N. I., Onopchuk Yu. N., Polinkevich K. B. Role of mechanisms of systemic regulation of respiration and blood circulation during intensive operator activity. *Kibernetika i vyčislitelnaâ tehnika*. 1995, Is. 106, P. 103–108. (In Russian).
  70. Onopchuk Yu. N., Navakatikyan A. O., Aralova N. I. Peculiarities of self-organization of cardiovascular system during intensive operator activity. Model studying. *Human problems — ecology, health, education: Materials 1<sup>st</sup> Intern. Council, May 18–21, 1995. Uzhgorod, Ukraine*. 1996, P. 116–120. (In Russian).
  71. Navakatikyan A. O., Marchenko D. I., Onopchuk Yu. N., Aralova N. I. Role of mechanisms of systemic regulation of respiration and blood circulation during intensive operator activity. *Hypoxia: destructive and constructive action. Mater. of Intern. Conference and Prielbrussie talks devoted to 50-th anniv. of research activity and 80-th anniv. of birthday of Prof., Dr. Sci. Kolchinskaya A. Z.* Kyiv, June 10–12, Terskol Aug. 6–12, 1998 p. (In Russian).
  72. Aralova N. I. Mathematical model of reliability of the function operator of the system of continuous interactions during temperature alteration. *Wshodnioeuropejskie Czasopismo Naukowe*. 2015, V. 1, P. 81–87.
  73. Aralova N. I. Software for studying of reliability of operator work under hightened situational stress. *Science and Innovation*. 2016, 12 (2), 15–25. <http://dx.doi.org/10/15407/scin12.02.015> (In Ukrainian).
  74. Aralova N. I., Mashkin N. I., Mashkina I. V. Reliability of the work of operators of human-machine system in conditions of high situational stress and temperature changes in environment. Study at mathematical model. *Mater. of 5-th Intern. Conference in Math. Modeling, Optimization and Information Technologies*. Kishiney, March 22–25, 2016, P. 22–32. (In Russian).
  75. Aralova N. I. Respiratory system's self-organization parameters of the operator of the system of continuous interaction for decision-making in a complex situational conditions. research on mathematical model. *Journal of Automation and Information Sciences*. 2020, V. 2, P. 83–98.
  76. Bobryakova I. L. Investigation of the task of optimal control with criterion of compromise conflicts resolution in complex situation condition during decisionmaking. *Kibernetika i vyčislitelnaâ tehnika*. 2002, Is. 135, P. 84–89 (In Russian).
  77. Aralova N. I., Klyuchko O. M., Mashkin V. I., Mashkina I. V. Compromise solution of conflict situations in the problem of optimal control in the design making under the complex situational conditions. *Electronics and control systems*. 2019, V. 2, P. 77–83. <https://doi.org/10.18372/1990-5548.52.13818>
  78. Aralova N. I. Research of role of hypoxia, hypercaphnia and hypometabolism in the regulation of the respiratory sytstem in their internal and external disturbances based on the mathematical model. *Kibernetika i vyčislitelnaâ tehnika*. 2017, V. 188, P. 49–64. <https://doi.org/10.15407/kvt188.02.049>
  79. Aralova N. I., Mashkin V. I. The control mechanism's research of the gas-exchange organizms function on the mathematical model of a functional system of respiration. *Theory of optimal solutions*. 2019, V. 18, P. 40–45.
  80. Bobriakova I. L. Mathematical modeling of hypometabolism process with the objective to identify peculiarities of human organism during the work under condition of highlands. *Kibernetika i vyčislitelnaâ tehnika*. 2014, V. 178, P. 64–69.
  81. Bobriakova I. L., Korniyush I. I., Mashkina I. V. Study of hypometabolism process during the work at highlands. *Computer mathematics*. 2014, N 2, P. 34–42.
  82. Bobriakova I. L., Mashkina I. V., Semchik T. A. Imitation of compensatory reactions of an organism for a hipercapnic stimulation. *Computer mathematics*. 2005, N 2, P. 94–103.
  83. Aralova N. I., Beloshitsky P. V. The change of the parameters of athlete's respiratory system during adaptation to the mountain meteorological factors. Research based on the mathematical models. *Sports Medicine*. 2016, V. 1, P. 111–116.
  84. Aralova N. I., Mashkin V. I., Mashkina I. V. Mathematical model of respiratory system short-term adaptation of persons working in extreme high mountain conditions. *Informatics and systemic sciences (ICH-2016): Mater. of VII All-Ukrainian Sci.-Pract. Conference with Intern. Participation (Poltava, March 10–12, 2016)*. Ed. Emetz O. O. Poltava: PUET. 2016, P. 29–31. Access: <http://dspace.puet.edu.ua/handle/123456789/2968> (In Russian).
  85. Aralova N. I., Shakhlina L. Ya.-G., Futornyj S. M., Kalytka S. V. Information technologies of grounding of optimal course of interval hypoxic training in practice of sports training of highly qualified sportsmen. *Journal of Automation and Information Sciences*. 2020, V. 1, P. 130–142.
  86. Aralova N. I., Klyuchko O. M., Mashkin V. I., Mashkina I. V. Algorithmic and program



- support for optimization of modes selection for pilots interval hypoxic training. *Electronics and control systems*. 2017, V. 2, P. 105–113. <https://doi.org/10.18372/1990-5548.52.11882>
87. *Shakhlina L. Ya-G., Aralova N. I.* Forecasting the organism reaction of the athletes on inhibiting hypoxic mixtures on the mathematical model of the functional respiration system. *Kibernetika i vychislitelnaâ tehnika*. 2018, V. 193, P. 64–82. <https://doi.org/10.15407/kvt193.03.064>
  88. *Aralova N. I., Klyuchko O. M., Shakhlina L. Ya-G.* Parameters Of Athlete Respiratory System Dependence On Organism Hormonal Status During Hypoxic Mixtures Inhalation: Research On Mathematical Models. *SF J. Sports Med.* 2018, V. 1, P. 2. <http://scifedpublishers.com/journals/scifed-journal-of-sports-medicine>
  89. *Aralova N. I., Shakhlina L. Ya-G.* The mathematical models of functional self-organization of the human respiratory system with a change of the hormonal states of organism. *Journal of Automation and Information Sciences*. 2018, V. 3, P. 132–141.
  90. *Aralova N. I., Mashkin V. I., Mashkina I. V.* Forecasting of fatigue development at mathematic model of respiratory system with optimal control. *Mater. of VI All-Ukrainian Sci.-Pract. Conference with Intern. Participation (Poltava, March 10–12, 2016.)* Ed. Emetz O. O. *Poltava: PUET*. 2016, P. 29–31. Access: <http://dSPACE.puet.edu.ua/handle/123456789/2392> (In Russian).
  91. *Kolchinskaya A. Z., Monogarov V. D., Aralova N. I.* About forecasting of fatigue development during intensive muscle activity. *Oxygen regimes of organism, work ability, fatigue during intensive muscle activity (Workshop materials). Part 1. Vilnius*. 1989, P. 111–125. (In Russian).
  92. *Onopchuk Yu. N., Kurdanov H. A., Semchik T. A., Aralova N. I., Beloshitsky P. V.* Mathematical research of oxygen insufficiency in an organism under an ischemic heart disease. *Computer Mathematics*. 2003, N 2, P. 152–159.
  93. *Beloshitsky P. V., Onopchuk Yu. N., Aralova N. I., Semchik T. A.* Mathematic modeling of hypoxic states at heart ischemia. *Physiol. J.* 2004, 50 (3), 139–143. (In Russian).
  94. *Semchyk T. A.* Models of development and compensation of hypoxic conditions under ischemic heart disease. *Theory of optimal solutions*. 2017, V. 16, P. 86–91.
  95. *Aralova N. I., Klyuchko O. M., Mashkin V. I., Mashkina I. V.* Mathematical models for development and compensation of hypoxic states during ischemic heart disease in flight crews' personnel. *Electronics and control systems*. 2019, V. 1, P. 80–90. <https://doi.org/10.18372/1990-5548.59.13644>
  96. *Aralova N. I., Mashkin V. I., Mashkina I. V.* Athletes heart hypertrophy as result of long-term adaptation to loadings. Studying at mathematical model. *Scientific achievements of modern society. Abstracts of the 5th International scientific and practical conference. Cognum Publishing House. Liverpool, United Kingdom*. 2020, P. 286–292. URL: <http://sci-conf.com.ua>
  97. *Aralova N. I.* Modification of respiration system mathematic model for the investigation of ischemic heart disease. *Informatics and systemic sciences (ICH-2017): Mater. of VII All-Ukrainian Sci.-Pract. Conference with Intern. Participation (Poltava, March 10–12, 2017)* Ed. Emetz O. O. *Poltava: PUET*. 2017, P. 29–31. Access: <http://dSPACE.puet.edu.ua/handle/123456789/2968> (In Ukrainian).
  98. *Aralova N. I., Vyschenski V. I., Onopchuk Yu. N.* Data models and algorithms for their treatment at the construction of integral of grade and performance of athletes. *Computer Mathematics*. 2013, V. 1, P. 151–160.
  99. *Onopchuk Yu. N., Aralova N. I., Beloshitsky P. V., Klyuchko O. M.* Mathematic models and integral estimation of organism systems reliability in extreme conditions. *Electronics and control systems*. 2015, V. 4, P. 109–115.
  100. *Aralova N. I., Klyuchko O. M., Mashkin V. I., Mashkina I. V.* Algorithms for data models processing for integral estimation of flight crews' personnel states. *Electronics and control systems*. 2018, V. 1, P. 99–105. <https://doi.org/10.18372/1990-5548.55.12788>
  101. *Onopchuk Yu. N., Aralova N. I., Beloshitsky P. V., Klyuchko O. M.* Integral estimation of human reliability and work ability during wrestling. *Bulletin of Engineering Academy of Ukraine*. 2015, N 3, P. 145–148. (In Russian).
  102. *Aralova N. I., Onopchuk Yu. N.* Dynamics of volumetric velocity of blood flow at physical loading of trained persons. Analysis of computational experiments with mathematical model. *Cybernetics*. 1990, N 3, P. 125–127. (In Russian).
  103. *Onopchuk Yu. N., Aralova N. I., Beloshitsky P. V., Podlivaev B. A., Mastucash Yu. I.* Forecasting of wrestler' state in the combat on the base of mathematic model of functional respiratory system. *Computer mathematics*. 2005, N 2, P. 69–79. (In Russian).
  104. *Aralova A. A., Aralova N. I., Kovalchuk-Khymyuk L. A., Onopchuk Yu. N.* Automated information system for athletes functional diagnostics. *Control systems and machines*. 2008, V. 3, P. 73–78. (In Russian).

105. Beloshitsky P. V., Onopchuk Yu. N., Aralova N. I., Podlivaev B. A. Mathematic forecasting of wrestler' state during combat. *Sport medicine*. 2009, N 1–2, P. 55–59. (In Ukrainian).
106. Aralova N. I., Onopchuk Yu. N., Podlivaev B. A. Mathematic models for control of sportive combat. *International Workshop "Prediction and Decision Making under Uncertainties (PDMU-2004)"*, Abstracts. Ternopil, Ukraine. 2004. (In Ukrainian).
107. Aralova N. I. Information technologies of decision making support for rehabilitation of sportsmen engaged in combat sport. *Journal of Automation and Information Sciences*. 2016, V. 3, P. 160–170.
108. Aralova A. A., Aralova N. I., Beloshitsky P. V., Onopchuk Yu. N. Automated Information System for Functional Diagnostics of Mountaineers. *Sports Medicine*. 2008, V. 1, P. 163–169.
109. Beloshitsky P. V., Klyuchko O. M., Onopchuk Yu. N. Results of investigations of adaptation problems by Ukrainian scientists in Prielbrussie. *Bulletin of NAU*. 2008, V. 1, P. 102–108. (In Ukrainian).
110. Onopchuk Yu. N., Beloshitsky P. V., Klyuchko O. M. Creation of mathematic models on the results of investigations of Ukrainian scientists at Elbrus. *Bulletin of NAU*. 2008, V. 3, P. 146–155. (In Ukrainian).
111. Beloshitsky P. V., Klyuchko O. M., Onopchuk Yu. N., Kolchinskaya A. Z. Results of investigations of high nervous activity by Ukrainian scientists in Prielbrussie. *Bulletin of NAU*. 2009, V. 2, P. 105–112. (In Ukrainian).
112. Beloshitsky P. V., Klyuchko O. M., Onopchuk Yu. N. Results of some medical and biological investigations of Ukrainian scientists at Elbrus. *Bulletin of NAU*. 2007, V. 3, P. 10–16. (In Ukrainian).
113. Beloshitsky P. V., Klyuchko O. M., Onopchuk Yu. N. Studying of hypoxia problem by Ukrainian scientists at Elbrus region. *Bulletin of NAU*. 2007, V. 2, P. 44–50. (In Ukrainian).
114. Beloshitsky P. V., Klyuchko O. M., Onopchuk Yu. N. Results of investigations by Ukrainian scientists of mountain factors influence on the health and life duration in Prielbrussie. *Bulletin of NAU*. 2008, V. 4, P. 102–108. (In Ukrainian).
115. Beloshitsky P. V., Klyuchko O. M., Onopchuk Yu. N. Results of investigations of structural and functional inter-relations by Ukrainian scientists in Prielbrussie. *Bulletin of NAU*. 2009, V. 1, P. 61–67. (In Ukrainian).
116. Aralova N. I., Klyuchko O. M., Mashkin V. I., Mashkina I. V. Mathematical models and integral estimation of organism systems reliability in extreme conditions. *Electronics and control systems*. 2016, V. 1, P. 107–115.
117. Aralova N. I., Klyuchko O. M., Mashkin V. I., Mashkina I. V. Investigation of reliability of operators work at fluctuating temperature conditions. *Electronics and control systems*. 2016, V. 2, P. 133–140.
118. Aralova N. I., Klyuchko O. M., Mashkin V. I., Mashkina I. V. Mathematical model for research of organism restoring for operators of continuously interacted system. *Electronics and control systems*. 2016, V. 3, P. 100–105.
119. Aralova N. I., Klyuchko O. M., Mashkin V. I., Mashkina I. V. Technical complex for selection, current medical control and rehabilitation of flight personnel members. *Mater. Sci.-Tech. Conference "Problems of development of global system for connections, navigation, monitoring and air flights organization CNS/ATM"*. November 21–23, 2016. Kyiv: NAU. 2016, P. 114. (In Ukrainian).
120. Aralova N. I., Klyuchko O. M., Mashkin V. I., Mashkina I. V. Mathematic modeling of functional self-organization of pilots' respiration. "Integrated intellectual robototechnical complexes". "IIRTC-2017": XI Conf. Mater. Kyiv: "NAU-druk". 2018, P. 268–269. (In Ukrainian).
121. Aralova A. A., Aralova N. I., Klyuchko O. M., Mashkin V. I., Mashkina I. V. Information system for the examination of organism adaptation characteristics of flight crews' personnel. *Electronics and control systems*. 2018, V. 2, P. 106–113. <https://doi.org/10.18372/1990-5548.56.12944>
122. Aralova A. A., Aralova N. I. Authomatized information system for the estimation of functional respiratory system. *Physiol. J.* 2008, 54 (4), P. 57. (In Russian).
123. Klyuchko O. M., Aralova N. I., Aralova A. A. Electronic automated work places for biological investigations *Biotechnol. acta*. 2019, 12 (2), 5–26. <https://doi.org/10.15407/biotech12/02/005>
124. Aralova N. I. Evaluation of respiratory functional system, oxygen regimes of human organisms and the degree of hypoxia (a set of programs for PC). *Physiol. J.* 1996, 42 (3–4), 96. (In Russian).
125. Aralova N. I., Mashkin V. I. The equations of inert gases dynamics for optimization of decision-making in providing safe decompression of the aquanaut. *Theory of optimal solutions*. 2018, V. 17, P. 62–68.
126. Aralova N. I., Mashkin V. I., Mashkina I. V. Information technologies for decisionmaking support for providing of aquanauts decompression security in

- conditions of hyperbaric hypoxia. *Mater. of 6-th Intern. Conferense "Mathematic modeling, optimization and information technologies"*, Kishiney, Moldova Republic, November 12–16, 2018. Kishiney: Evrika. 2018, P. 248–251. (In Russian).
127. Beloshitskiy P. V., Onopchuk Yu. N., Aralova N. I. Mathematical models of respiratory systems and circulation of the blood systems as well as the estimation of organism's reserves and of the reliability of system's function. *Eur. J. Physiol.* 1995, Supp. to 430 (4). (Abstracts of the of the First FEPS Congress 9–12 Sept., 1995, Maastricht, The Netherland).
128. Aralova N. I., Mastykash Yu. I., Mashkina I. V. Information technologies for the studying of work ability reserves of human organism during the work in extreme high mountain conditions. *Mater.Conf. "Information problems of computer systems, jurisprudence, energetics, economy, modeling and management Step to the Science. Collection of research works of Buchach Institute of Management. Buchach.* 2011, V. 7, P. 195–198. (In Ukrainian).
129. Aralova N. I., Mashkina I. V. Studying at mathematic models of organism adaptation possibilities for changed environmental conditions. *Combinatory optimization and fuzzy multitudes: (COFM-2013). Mater. of III All-Ukrainian Sci. Seminar (Poltava, August 30–31, 2013).* Ed. Dr. Sci., Prof. O. O. Emetz. *Poltava: PUET.* 2013, P. 5–7. (In Russian).
130. Aralova N. I. Mathematical models of estimation of depletion of functional systems of human body after exposure to hypoxia hypermetabolic and effectiveness correction. *X Intern. Sci.-Pract. Conference "Domestic Science in Epoque of Changes: Postulates of the Past and Theories of New Time", part 7.* 2015, V. 10, P. 7–11. (In Russian).
131. Aralova N. I., Beloshitsky P. V., Klyuchko O. M. Mathematical models of system mechanisms of organism adaptation to hypoxia *Abstracts 7<sup>th</sup> Chronic Hypoxia Symposium Feb 23–Mar 2, 2019.* La Paz. Bolivia Dedicated to the Late Danish Prof. Poul Erik Paulev. P. 24. <https://zuniv.net/symposium7/Abstracts7CHS.pdf>
132. Marchenko D. I., Byts A. V., Semchik T. A. A multicriterial problem of system blood stream distribution in organs and tissues and an algorithm to its solution. *Cybernetics and system analysis.* 2001, V. 5, P. 132–141.
133. Aralova N. I. Mathematical models of decision support by the training in extreme conditions. *IX Intern. Sci.-Pract. Conference "Domestic Science in Epoque of Changes: Postulates of the Past and Theories of New Time", part 7.* 2015, V. 9, P. 7–9.
134. Aralova N. I. Information means for optimizing the process of athlete body recovery. *Sports Medicine and physical rehabilitation.* 2017, V. 1, P. 88–96.
135. Marchuk G. I., Pogozhev I. B., Zuev S. M. Similarity conditions in systems of interacting particles. *Doc. RAS.* 1995, 345 (5), 605–606.
136. Belykh L. N. Analysis of some mathematical models in immunology. *Moskva: OVM AN USSR.* 1984, 147 p.
137. Marchuk G. I., Petrov R. V., Romanyukha A. A., Bocharov G. A. Mathematical model of antiviral immune response. I. Data analysis, generalized picture construction and parameters evaluation for Hepatitis B. *J. Theor. Biol.* 1991, 151 (1), 1–40.
138. Liashko N. I., Onopchuck G. Yu. Pharmacological correction of organism state. Mathematical model and its analysis. *Computer Mathematics.* 2005, V. 1, P. 127–134. (In Russian).



## ІНТЕГРОВАНА МАТЕМАТИЧНА МОДЕЛЬ ДЛЯ ІМІТАЦІЇ ПЕРЕБІГУ ВІРУСНОГО ЗАХВОРЮВАННЯ ТА КОРЕКЦІЇ СПРИЧИНЕНОГО НИМ ГІПОКСИЧНОГО СТАНУ

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Метою роботи було створення комплексної математичної моделі, що імітує перебіг захворювання, спричиненого вірусом SARS-CoV-2, та фармакологічної корекції гіпоксичних станів організму в разі ускладнення цього захворювання. В цій роботі було використано методи математичного моделювання та теорії оптимального керування рухомими об'єктами. Запропонована математична модель складалася з математичних моделей функціональних систем дихання та кровообігу, терморегуляції, імунної відповіді, еритропоезу та фармакологічної корекції. Для цієї моделі було взято індивідуальні дані пацієнта і здійснено імітацію вірусного захворювання. Прогнозували реакції органів дихання та кровообігу: розраховано парціальний тиск дихальних газів у альвеолярних просторах та їхню напругу в крові легеневих капілярів, артеріальної та змішаної венозної крові та тканинної рідини. Далі імітували ін'єкцію антигіпоксанта та розраховували значення тих самих параметрів. Таким чином можна було вибрати найбільш оптимальний спосіб корекції гіпоксичного стану для будь-якої людини. На сьогодні ця модель є суто теоретичною, оскільки моделі системи дихання та кровообігу було розроблено на усереднені дані, і вони не враховують особливостей окремих осіб, інфікованих SARS-CoV-2. Зокрема, це стосується газообміну в альвеолярному просторі можливих особливостей проникності дихальних газів через альвеолярно-капілярну мембрану. Однак це один із можливих напрямів вирішення складних завдань, пов'язаних з лікуванням захворювання, спричиненого вірусом SARS-CoV-2. У результаті було розроблено комплекс інформаційної підтримки для імітації перебігу вірусних захворювань, а також фармакологічної корекції спричинених ними гіпоксичних станів.

**Ключові слова:** вірус SARS-CoV-2, модель імунного відгуку, математична модель дихальної системи, гіпоксичний стан, інфекційне ураження.

## ИНТЕГРИРОВАННАЯ МАТЕМАТИЧЕСКАЯ МОДЕЛЬ ДЛЯ МОДЕЛИРОВАНИЯ ТЕЧЕНИЯ ВИРУСНОГО ЗАБОЛЕВАНИЯ И КОРРЕКЦИИ ВЫЗВАННОГО ИМ ГИПОКСИЧЕСКОГО СОСТОЯНИЯ

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Целью работы было создание комплексной математической модели, имитирующей течение заболевания, вызванного вирусом SARS-CoV-2, и фармакологической коррекции гипоксических состояний организма, возникающих в случае осложнения этого заболевания. В этой работе использовались методы математического моделирования и теории оптимального управления движущимися объектами. Предлагаемая математическая модель состояла из математических моделей функциональных систем дыхания и кровообращения, терморегуляции, иммунного ответа, эритропоеза и фармакологической коррекции. Для этой модели были взяты индивидуальные данные пациента и смоделирован эффект в виде вирусного заболевания. Спрогнозированы реакции дыхательной и кровеносной систем: рассчитаны парциальное давление дыхательных газов в альвеолярных пространствах и их напряжение в крови капилляров легких, артериальной и смешанной венозной крови и тканевой жидкости. Далее имитировали инъекцию антигипоксанта и рассчитывали значения тех же параметров. Таким образом можно было выбрать наиболее оптимальный способ коррекции гипоксического состояния для среднестатистического человека. На сегодняшний день эта модель является чисто теоретической, поскольку модели системы дыхания и кровообращения были разработаны усредненные данные, и не учитывающие особенности отдельных лиц, инфицированных SARS-CoV-2. В частности, это касается газообмена в альвеолярном пространстве и возможных особенностей проницаемости дыхательных газов через альвеолярно-капиллярную мембрану. Однако это одно из возможных направлений решения сложных задач, связанных с лечением заболевания, вызванного вирусом SARS-CoV-2. В результате был разработан комплекс информационной поддержки для имитации течения вирусных заболеваний, а также фармакологической коррекции вызванных ими гипоксических состояний.

**Ключевые слова:** вирус SARS-CoV-2, модель иммунного отклика, математическая модель дыхательной системы, гипоксическое состояние, инфекционное поражение.