UDC 519.8.612.007 https://doi.org/10.15407/biotech13.05.005

MATHEMATICAL MODELLING OF IMMUNE PROCESSES AND ITS APPLICATION

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Received 11.07.2020
Revised 07.10.2020
Accepted 31.10.2020

The aim of the study was to develop a mathematical model to research hypoxic states simulation of an organism infectious lesions. The model is based on the methods of mathematical modeling and the theory of optimal control of moving objects. The processes of organism damage are simulated with the mathematical model of immune response developed by G.I. Marchuk and the members of his scientific school, adapted to current conditions. This model is based on Burnet's clone selection theory of the determining role of antigen. Simulation results using the model are presented. The dependencies of infectious courses on the volumetric velocity of systemic blood flow is analyzed on the complex mathematical model of immune response, respiratory and blood circulation systems. The immune system is shown to be rather sensitive to the changes in blood flow via capillaries. Thus, the organ blood flows can be used as parameters for the model by which the respiratory, immune response, and blood circulation systems interact and interplay.

Key words: mathematical model of immune response, functional respiratory system, simulation of infectious disease course, integrated mathematical model, interaction of functional systems of organism.

General approaches to the mathematical modeling of immune processes

Recent results in areas such as molecular biology, human genetics, clinical and experimental immunology have helped to understand the leading role of immune defense mechanisms in the pathogenesis of infectious diseases. In particular, fundamental knowledge has been obtained in clinical immunology that reflects the patterns of the immune system response to infectious diseases [1–3]. An important milestone was the discovery of the universal nature of the processes of immune defense, namely the recognition, learning and memory. And the development and improvement of computer technology has contributed to the creation of appropriate mathematical models [4–9].

Currently, the immunological research developed a significantly deeper knowledge about the structural characteristics of the immune system, the regulation of the activity of its individual components, which function as a holistic distributed system. Mathematical modeling is an analytical tool for describing, analyzing and predicting the dynamics of immune responses under a reductionist approach. Building mathematical models of the human immune system that reflect the obtained understanding of its structure and describe the processes that determine it functionally is an urgent task for modern systemic immunology and its new interdisciplinary field, mathematical immunology. Grebennikov et al. [10] emphasize the need for systematic development of multiscale mathematical models that describe the development of immune responses at different detailization: intracellular regulation of the components of immune system activity, population dynamics of cells

in organs and systemic immunophysiological processes in the whole organism.

The mathematical modeling of infectious diseases is one of the important areas of implementation of mathematical methods in immunology and medicine. This area of research emerged about 40 years ago and is evolving through the efforts of different groups of researchers from different countries. Significant progress has been made in research of the process of anti-infective immunity, which is still the subject of comprehensive theoretical studies [11–13]. The work of Hege and Cole is considered to be one of the first works in the field of modeling of immune processes [14]. The authors proposed an equation describing the change in the number of circulating antibodies depending on the number of plasma cells. Cohen in his works [15,16] proposed the concept of activation and suppression signals to describe the switching and paralysis of the immune process.

Notably, two different approaches to the mathematical description of the immune defense process have been formed. One of them is based on the assumption of the leading role of antigen and is a mathematical formulation of Burnet's clone selection theory. The other is based on Erne's hypothesis, i.e. the principle of network regulation of interactions between different populations of immune system cells and viral antigen. Hereafter, we consider an approach1 based on Burnet's clone selection theory because Erne's theory exists today only as a hypothesis, although there are a number of publications related to the mathematical modeling of that theory.

Mathematical modeling of Burnet's clone selection theory

The first most detailed study of the mathematical description of clone selection was made by the American researcher Bell. In his work, Bell [17] using the main hypotheses of Burnet's clone selection theory has built a mathematical model of the humoral immune response to a non-reproducing monovalent antigen. He has further modified the model for the case of heterogeneous antibodies and multivalent antigen [18, 19], and in [20] has proposed the simplest model of immune response to reproducing antigen, in which the interaction between antigen and antibody was described in terms of "predator-victim".

Pimbley has studied the behavior of Bell's model [21–23]. Pimbley has considered not only the two-dimensional but also the three-dimensional model with the inclusion of plasma cells and proved the existence of stable periodic solutions in each of these variants.

Smirnova and Stepanova [24–26] have also considered modeling the immune response. Their models were based on Sekarts-Koons's hypothesis. Immunocompetent cells were thought to transform into lymphoblasts after first contact with the antigen. Several times upon repeated contact with the antigen, the dividing cells are transformed into plasma cells, which in turn produce antibodies. If there is no repeated contact, they become memory cells.

Sekarts-Koons's hypothesis became the basis for studies by Jilek [27–29], who analyzed in detail the interaction of antigen with lymphocytes. He proposed a number of probabilistic models for different cell types that repeatedly contacted with a specific antigen.

Mohler in his works [30–32] continued and generalized the ideas that were the basis of Bell's model. In [30], he has considered the case of the production of two classes of antibodies Ig M and Ig G. "Switching" antibody synthesis occurs over a period of time that depends on the antigen's concentration in the body. The concentration of these cells is the initial condition in the simulation of second response. Mohler investigates *T*- and *B*-systems of immunity and the principles of their cooperation in the process of antibody formation. The author also considers a model that reflects the course of the immune process in various organs and systems of the body: in the blood, lymph nodes, spleen. This model is a combination of bilinear schemes, each of which reflects the dynamics of the process components in the corresponding organ.

Italian scientists Bruni, Giovenco, Koch, and Strom have proposed a model of humoral response [33, 34] describing the heterogeneity of the immunocyte population using the continuous functions of the two arguments of affinity and time. This model is a system of five integral-differential equations that describe the dynamics of *B*-immunocytes, *B*-plasma cells, antibodies, the immune complex, and the nonproliferating antigen. It is assumed that *B*-immunocytes are generated, and the rate of their generation depends on the affinity distribution of cellular receptors. The immune system in these models was considered from the standpoint of the theory of bilinear systems. A series of works is devoted to modeling the immune response to a reproducing antigen, i.e. the response against bacteria, viruses

and tumors. The immune response against bacteria was studied in [35–41]. The case of cellular immune response against tumors was considered in [42–44].

The basic principles of mathematical modeling of the immune response and infectious diseases were formulated by Marchuk in building a basic model of infectious disease in 1975. The dynamics of populations of viruses, plasma cells and antibodies, and the characteristics of the degree of damage to the target organ were considered in this model, based on a system of nonlinear differential equations with delay. The main task of this model was to describe the disease as a physical process of interaction of cells and molecules of the immune system, target organ and pathogen. By the time the basic model of infectious disease emerged, mathematical models of the immune response have already been developed [4, 14, 17, 20, 27].

However, the model proposed by Marchuk has a number of features that distinguish it from others and allow it to be used in theoretical studies of the immune system. First, Burnet's clone selection theory, which still retains the importance of a fundamental element of modern immunology, was used as the basic mechanism of the immune response. Second, the introduction into the model of a variable m (a quantity that describes the degree of damage to the target organ) transforms the model of the immune response into a model of infectious disease.

Thirdly, the model uses delayed equations, allowing a more accurate description of the dynamics of the immune response. Finally, a function m was introduced into the model that reflects a decrease in the intensity of the immune response due to significant damage to the target organ. The mathematical model of Marchuk-Petrov [45] describes the dynamics of viral damage and immune response by a more complete system of differential equations, taking into account in the form of delays in the duration of cell division of the immune system. The monograph [46] presents models of experimental viral infections and mathematical models of viral hepatitis.

In the works of Asachenkov [47, 48], Belykh [49, 50], Romanyukha [51–53], and Bocharov [54–56], the basic model was used to study the most general laws of the dynamics of immune defense, as well as to analyze various variants of viral and bacterial infections, including mechanisms of infectious diseases in the chronic state, treatment of chronic forms of infections, study of the severity of viral hepatitis to variations in the parameters of the virus in the body, optimal management of infections [57–59]. Although the model equations describe the development of a humoral immune response in infectious diseases, the principles of constructing the basic model equations reflect a universal approach to modeling infectious diseases. This allowed us to successfully use both the model itself and its modifications for the analysis of various infections (influenza, viral hepatitis, pneumonia, chronic bronchitis, bronchial asthma, tuberculosis, mixed infections, etc.).

A number of studies describe the development of HIV in the human body [60–64]. The effect of antigenic load on the aging of the immune system was also studied [52, 65]. Antigenic load is understood as the total flow of molecules of biological nature, which enter the lymphatic tissue and cause immune response processes. To describe the dynamics of aging of the immune defense, a mathematical model of age-related changes in the properties of peripheral T-lymphocytes [66], and the models presented in [53] were used. As a result of modeling the estimation of severity of a course of pneumonia for various age categories is received. In [67], the immune system is presented as a complex dynamic and multilevel biological system that protects organisms from pathogen invasion and tumor development, and plays an active role in tissue homeostasis and organ regeneration. In [68], a mathematical model describing the antiviral immune response is considered, taking into account the interacting regulatory effects of the immune and neuroendocrine systems, and is based on the description of the manifestations of these effects [69–73]. The model takes into account the spatial organization of immune and infectious processes in various organs and tissues, for which the delay time of the interaction of components is introduced. The model consists of a system of 18 ordinary differential equations with a delayed argument; system parameters characterize the speed of various processes that affect the dynamics of infection. Chirkov's works are also notable [74, 75], stating that the correct formulation and solution of the problem of immune response management can significantly affect the correct choice of treatment, as well as the theoretical studies of the immune response. That is why Rusakov and Chirkov [76, 77] set the task of controlling the immune response in conditions of uncertainty.

Mai, Wang et al. [78] considered the prediction of treatment outcomes using mathematical models of the immune response to infection. They have revealed a fundamental limit to the accuracy of predicting results for a general class of mathematical models of the immune response to infection. It is noted that the accuracy of the forecast can be improved in the case of a slow forecast. Several systems of ordinary differential equations that simulate the host's immune response to pathogen load have been studied. The observed advantage of such systems of equations to study the immune response to infection is the ability to collect data on a large number of "virtual patients", each with a given set of parameters, and obtain many time points during the course of infection. It is noted that the combination of forecasting results with the treatment regimen is another important approach.

Kuznetsov and Shishkin [79–82] have summarized the data on the proliferation and differentiation of *Th*, *Tc* and *B*-lymphocytes in the form of mathematical models that give a holistic and detailed description of the processes of immune response, which allows to study the patterns of immune system and simulate the development of complex diseases to study their pathogenesis and etiology. The mechanisms of rubella, a complex autoimmune disease, were studied using the developed mathematical model and software.

Quiruette et al. [83] have considered the influence of diffusion and advection on the kinetics and localization of infection. The mathematical model in this study presents human airway as a one-dimensional pathway where stationary cells interact with the influenza virus. A platform is proposed to study the localization and spread of respiratory viral infections within the human respiratory tract. However, the paper does not take into account the complex structure of airways, which, according to Weibel's model [84], are dichotomously divided and divided into 23 generations.

A number of works primarily related to the names of Bocharov and Grebennikov [85–92] are also of note on modeling viral infection and the dynamics of viral response.

Eftimie, Gillard, Cantrell [93] have reviewed chosen areas of research in the field of mathematical immunology, which have developed recently, based on current advances in genetics, biochemistry and experimental and clinical immunology. A significant number of mathematical models have been developed in recent decades. The review is well structured. To emphasize the complex, multiscale dynamics of the immune response, the study used a step-by-step approach to discuss a number of models obtained to study the dynamics of both innate and adaptive immune responses at the molecular, cellular, and tissue levels. The mathematical tools used to study these models were also discussed, as well as some future trends and prospects for both experimental and mathematical immunology. Beauchemin, Handel [94] have presented an overview of mathematical models of influenza A in the host organism or cell structure.

There are now developments in the mathematical modeling of coronavirus infection [95], which are based on the clinical characteristics of patients affected by SARS-CoV-2 [96–99]. The model was tested on well-studied influenza viruses and then compared the pathogenesis of two viruses. The interaction between congenital and adaptive host immune responses has been found to be a potential cause of more severe course and mortality in patients with COVID-19, in particular the time mismatch between the two immune responses has a major impact on disease progression. The authors suggest that temporarily suppressing the adaptive immune response and preventing its effects on innate immunity may allow innate immunity to get neutrolize of the virus more effectively.

Integrated mathematical model of the functional system of respiration, blood circulation, thermoregulation and immune protection

A simulation model [100] considered an infectious disease, the course of which is controlled by the immune system, as one of the types of disturbances in the circulatory system. To study the dynamics of infectious disease and the impact of the circulatory system on this process we used a mathematical model of the functional respiratory system (FRS) of the body [101–104] in combination with the immune response model [11], which allowed to investigate the role of systemic circulation when simulating the course of an infectious disease [105, 106]. This approach is justified also because the reliability of the body depends on the reliability of its respiratory and circulatory systems [72–75]. This approach was further developed into an integrated mathematical model simulating the course of infectious disease and compensation of obtained hypoxic conditions through pharmacological correction [111–113].

The aim of this work was to study the dependence of the course of an infectious disease on the volume velocity of the systemic circulation on a complex mathematical model of immune protection.

The mathematical model of immunity in general can be written as follows:

Let V be the number of antigens, m the relative characteristic of the damaged organ, F — the concentration of antigens, C — the concentrations of plasma cells. Then the dynamics of the immunodeficiency process, according to [105] can be formulated as:

$$\frac{dV}{dt} = (\beta - \gamma \cdot F) \cdot V,$$

$$\frac{dC}{dt} = \varepsilon(m) \cdot \alpha \cdot F(1-\tau) \cdot V \cdot (t - \tau) - \mu_C (C - C^*),$$

$$\frac{dF}{dt} = \rho C - (\mu_f + \eta \cdot \gamma \cdot V) \cdot F,$$

$$\frac{dm}{dt} = \sigma \cdot V \cdot (1 - m) - \mu_m m,$$

and the criterion of self-organization

$$\int_{t^*}^{t^{**}+\Delta t} [\rho_1 \sum_{i=1}^{n} \lambda_i (G_{t_i} O_2(\xi) - q_{t_i} O_2(\xi))^2 + \rho_2 \sum_{i=1}^{n} \lambda_i (G_{t_i} CO_2(\xi) + q_{t_i} CO_2(\xi))^2 + \rho_3 \sum_{i=1}^{n} \lambda_i (G_{t_i} N_2(\xi))^2 + \rho_4 f_k^2 (m(\xi), V(\xi))] d\xi,$$

where $f_k(m(\xi), V(\xi))$ is the function that characterizes the degree of virus damage to the target organ of k-tissue reservoir, ρ_4 is the coefficient grading the influence of the type of disease being simulated on the level of gas homeostasis, where $G_{t_i}O_2(\xi)$, $G_{t_i}CO_2(\xi)$, $G_{t_i}N_2(\xi)$ are flows of oxygen, carbon dioxide and nitrogen through the capillary tissue membranes of i tissue at ξ time, $q_{t_i}O_2(\xi)$, $q_{t_i}CO_2(\xi)$ are rates of oxygen utilization and removal of carbon dioxide from i tissue, λ coefficients characterize the vital importance of the body, and ρ coefficients characterize the sensitivity of the body to hypoxia, hypercapnia and excess nitrogen [101, 102, 114–116]. Fig. 1 presents a general view of a complex mathematical model of the relationship and interaction of functional systems of the body to simulate the course of an infectious disease.

Analysis of the results of computational experiments to study the role of blood circulation in infectious diseases of the body

The mathematical model of immunity was studied to determine the response of the main parameters of the immune system depending on changes in α, β parameters of the model, etc. It was assumed that at the initial moment of time t_0 : $V(t_0) = 0.001$, $m(t_0) = 0$, $F(t_0) = 1$, $(t_0) = 1$. It was also found that the behavior of the model is quite stable with respect to its main parameters. A series of experiments was performed to study the effect of blood circulation through the capillaries of the target organ tissues on the course of infectious disease in the body. Fig. 2–5 present the results of computational experiments reflecting the behavior of the basic parameters of the immune system m, V, C, F, obtained by simulating the processes under different conditions of blood

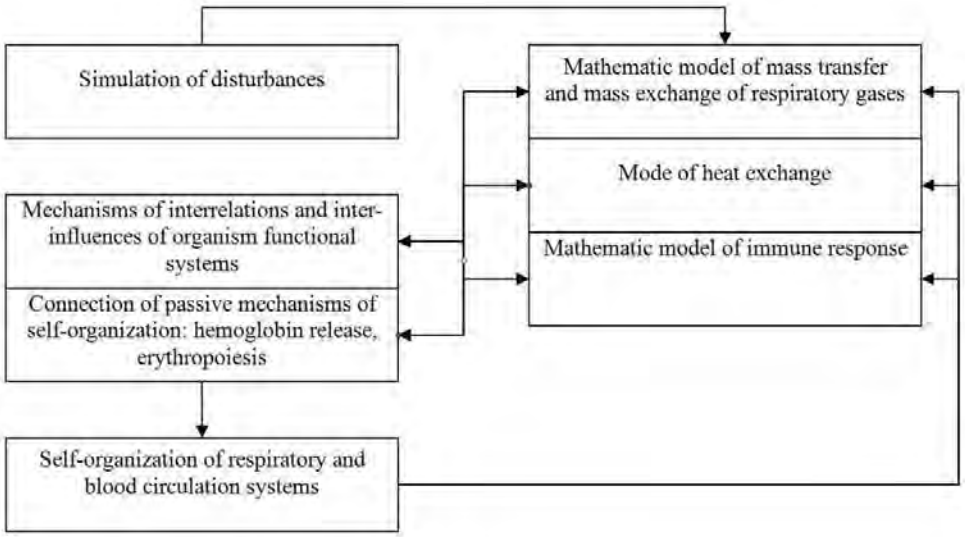

Fig 1. **Complex mathematical model of functional systems of an organism**

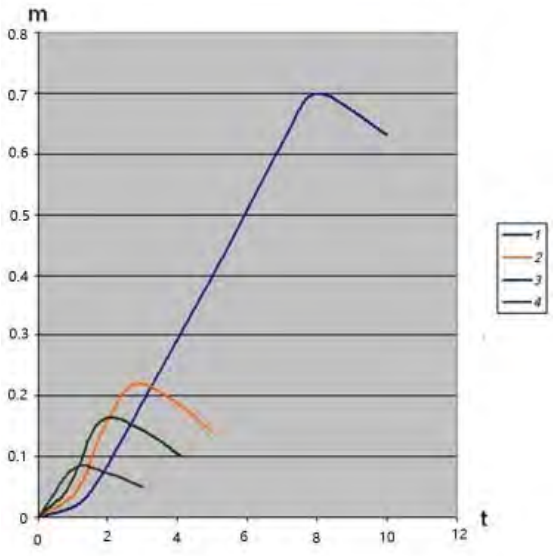

Fig. 2. **Dynamics of $m(t)$ (relative characteristics of the affected organ) under different conditions of blood circulation in the capillaries of the target organ:**
1 — $n_k = 0.5$; *2* — $n_k = 0.9$; *3* — $n_k = 1$; *4* — $n_k = 1.5$

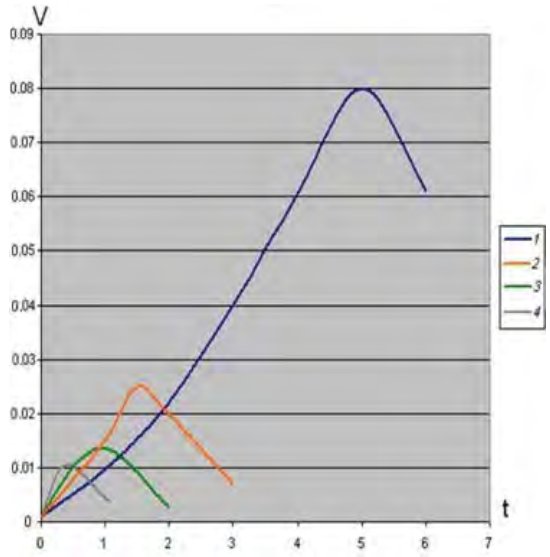

Fig. 3. **Dynamics of (concentration of pathogenic antigens) under different circulatory conditions in the capillaries of the target organ:**
1 — $n_k = 0.5$; *2* — $n_k = 0.9$; *3* — $n_k = 1$; *4* — $n_k = 1.5$

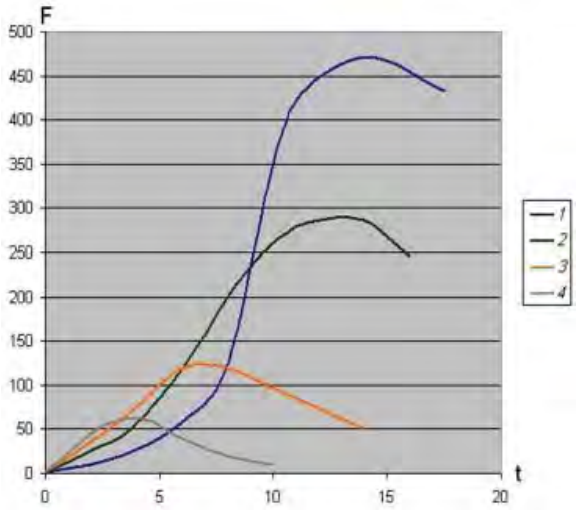

Fig. 4. **Dynamics of (concentration of antibodies) under different conditions of blood circulation in the capillaries of the target organ:**
1 — $n_k = 0.5$; *2* — $n_k = 0.9$; *3* — $n_k = 1$; *4* — $n_k = 1.5$

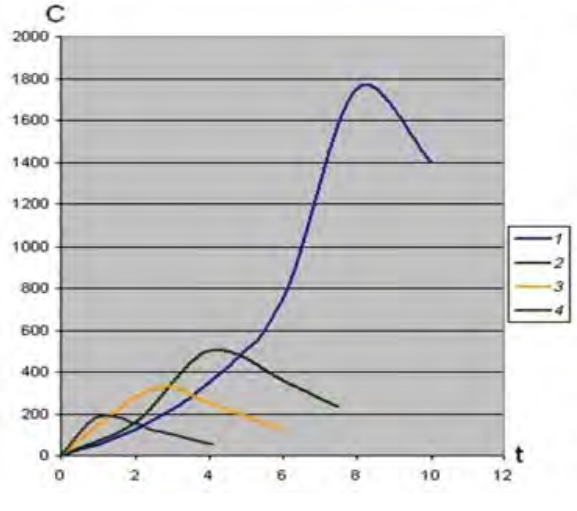

Fig. 5. **Dynamics of $C(t)$ (concentrations of plasma cells) under the different blood circulatory conditions in capillaries of the target organ:**
1 — $n_k = 0.5$; *2* — $n_k = 0.9$; *3* — $n_k = 1$; *4* — $n_k = 1.5$

supply to the target organ. This was ensured by setting the value n_k, the degree of change in tissue circulation relative to the "norm" ($n_k = Q_{t_k}/Q^0_{t_k}$).

It was determined that the transients in the parameters of the model of the immune system are faster, and the maximum levels of these parameters decrease with increasing blood circulation through the capillaries of the tissues of the target organ (Fig. 6, 7). Graphical dependences for m, V, C, F (Fig. 6–9) were obtained analyzing the results of computational experiments under given initial conditions for the model of the immune system and different levels of blood circulation through the capillaries of the target

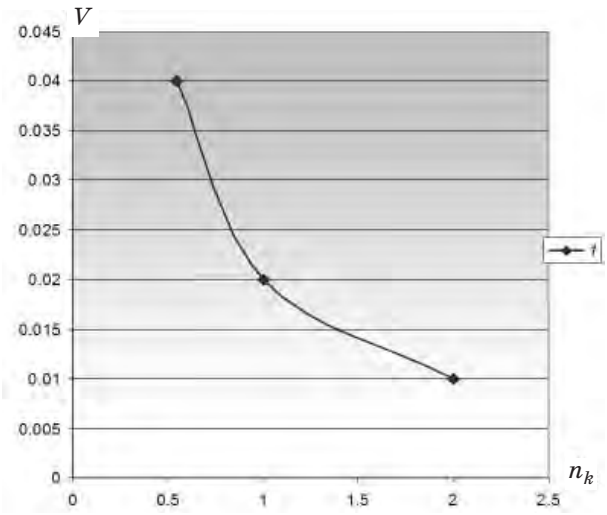

Fig. 6. **The nature of the change in *V* (concentration of pathogenic antigens) depending on the blood circulation through the capillaries of the target organ under given initial conditions for the development of infectious disease**

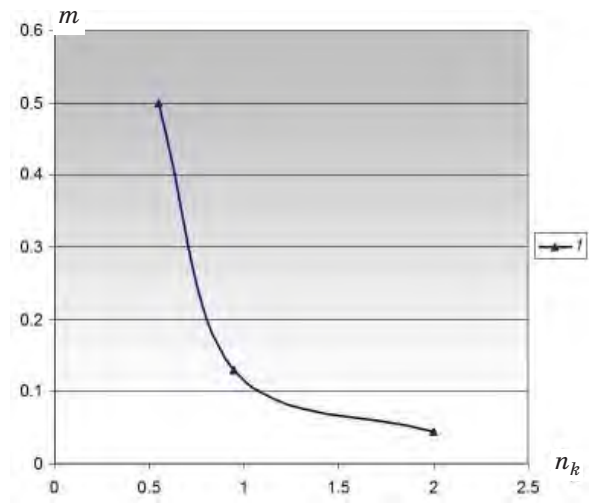

Fig. 7. **The nature of the change in *m* (relative characteristics of the affected organ) depending on the blood circulation through the capillaries of the target organ under given initial conditions for the development of infectious disease**

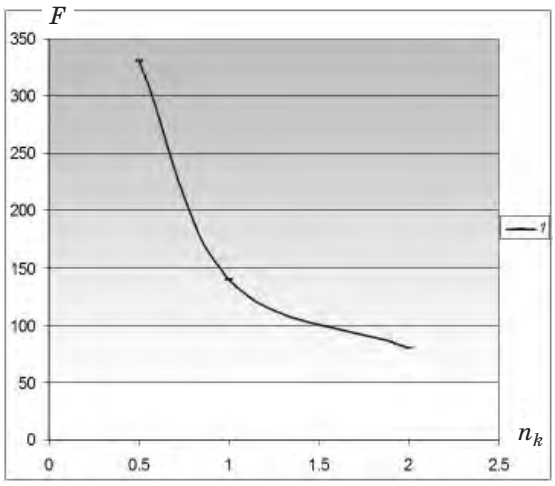

Fig. 8. **The nature of the change in *F* (antibody concentration) depending on blood circulation through the capillaries of the target organ under given initial conditions for the development of infectious disease**

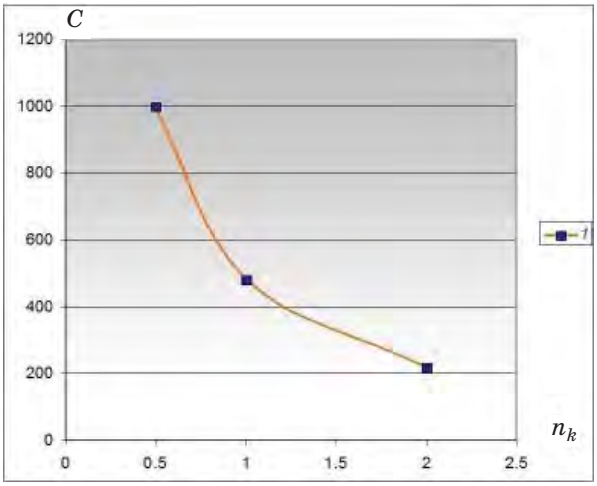

Fig. 9. **The nature of the change in *C* (concentration of plasma cells) depending on blood circulation through the capillaries of the target organ under given initial conditions for the development of infectious disease**

organ tissues. The experiments assumed that the multiplication factor of antigen (β), the coefficient determining the probability of neutralization of antigen by antibody (*y*), the stimulation factor of the immune system (*a*), the rate of antibody production by plasma cells (ρ), the values μ_c, μ_f are time of inverse lifespan of plasma cells and antibodies, the rate of damage to the target organ (σ) and the rate of recovery of the mass of the affected organ (μ_m) clearly depend on the degree of change in blood circulation through the capillaries of the tissues of the target organ. Based on studies of the biochemistry of processes occurring in the infected body, Pogozhev has proposed the following relations for the parameters of the body's immune status model [117]:

$$\beta = \bar{\beta} n_k^2, \gamma = \bar{\gamma} n_k^5, \alpha = \bar{\alpha} n_k^5,$$
$$\rho = \bar{\rho} n_k^2, \mu_c = \bar{\mu}_c n_k^2, \mu_f = \bar{\mu}_f n_k^2, \quad \sigma = \bar{\sigma} n_k^2, \mu_m = \bar{\mu}_m n_k^2,$$
$$\bar{\beta} = 2, \bar{\gamma} = 0.8, \bar{\alpha} = 10^4, \bar{\rho} = 0.17, \quad \bar{\mu}_c = 0.5, \bar{\mu}_f = 0.17, \bar{\sigma} = 10, \bar{\mu}_m = 0.12$$

The number of antibodies required to neutralize one virus was assumed to be 10. It was assumed that η does not depend on n_k. Time t_c of the formation of the cascade of plasma cells was determined by the formula:

$$t_c = \bar{t}_c / n_k^2$$

where $\bar{t}_c = 0.5$ day.

Continuous non-increasing function $\xi(m)$, $0 \le \xi(m) \le 1$, which characterizes the degree of disruption of the normal functioning of the immune system due to significant damage to the target organ, was given following [118]:

$$\xi(m) = \begin{cases} 1, m \le m^*, \\ \dfrac{1-m}{1-m^*}, m^* = 0.1, \end{cases}$$

where m^* is the the level of damage to the target organ, at which the activity of the immune system begins to decline.

Thus the approaches to mathematical modeling of immune processes are analyzed. A complex mathematical model of the human body is presented, which in particular includes a mathematical model of immune defense based on a mathematical description of Burnet's clone selection theory in the form of a system of nonlinear differential equations with delay, in which the population dynamics of viruses, plasma cells, antibodies and target organ's damage characteristics are considered.

The main task of this model was to consider the description of the disease as a physical process of interaction of cells and molecules of the immune system, the target organ and pathogen under study. The dependence of the course of an infectious disease on the volume velocity of the systemic circulation was investigated using complex mathematical model, which includes mathematical models of the functional system of respiration and blood circulation, immune response thermoregulation, and erythropoiesis.

We analyzed the dynamics of the main parameters that characterize the course of infectious disease and that are obtained in computational experiments with the immune model under different circulatory conditions in the capillaries of the target organ. It was revealed that the immune system is quite sensitive to changes in blood circulation through tissue capillaries and therefore organ circulation can be considered control parameters in the model. The results of computational experiments show that at low levels of viral damage to the target organ, complete and rapid recovery can be provided by a corresponding change in the circulatory system in the body.

The study was funded under the theme "To develop mathematical models of the integration organisms of functional systems for a body and methods of integration of their mathematical models to maintain the reliability and safety of human life in extreme conditions" (State registration — 0115U002573), 2015-2017. Research work 170.10). The authors declare no conflict of interests.

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МАТЕМАТИЧНІ МОДЕЛІ ІМУННИХ ПРОЦЕСІВ ТА ЇХ ЗАСТОСУВАННЯ

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Метою роботи було розробити математичну модель для дослідження гіпоксичних станів за імітації інфекційного ураження організму. Модель засновано на методах математичного моделювання і теорії оптимального управління рухомими об'єктами. Для імітації процесу ураження організму було застосовано математичну модель імунного відгуку, розроблену Г. І. Марчук і учнями його наукової школи, адаптовану до сучасних умов. Ця модель базується на теорії відбору клонів Барнета про визначальну роль антигену. Наведено результати моделювання з використанням такої моделі. Залежність перебігу інфекції від об'ємної швидкості системного кровотоку аналізується на комплексній математичній моделі імунного відгуку, системи дихання і кровообігу. Показано, що імунна система дуже чутлива до змін кровотоку в капілярах. Таким чином, потоки крові в органах можна використовувати як параметри моделі, за допомогою якої реалізується взаємодія системи дихання, імунного відгуку і кровообігу.

Ключові слова: математична модель імунного відгуку, функціональна система дихання, імітація перебігу інфекційного захворювання, інтегрована математична модель, взаємодія функціональних систем організму.

МАТЕМАТИЧЕСКИЕ МОДЕЛИ ИММУННЫХ ПРОЦЕССОВ И ИХ ПРИМЕНЕНИЕ

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Целью работы была разработка математической модели для исследования гипоксических состояний при имитации инфекционного поражения организма. Модель основана на методах математического моделирования и теории оптимального управления движущимися объектами. Для имитации процесса поражения организма использовалась математическая модель моделью иммунного отклика, разработанной Г. И. Марчуком и учениками его научной школы, адаптированная к современным условиям. Эта модель базируется на теории отбора клонов Барнета об определяющей роли антигена. Приведены результаты моделирования с использованием такой модели. Зависимость течения инфекции от объемной скорости системного кровотока анализируется на комплексной математической модели иммунного отклика, системы дыхания и кровообращения. Показано, что иммунная система весьма чувствительна к изменениям кровотока по капиллярам. Таким образом, потоки крови в органах можно использовать в качестве параметров модели, с помощью которой реализуется взаимодействие системы дыхания, иммунного отклика и кровообращения.

Ключевые слова: математическая модель иммунного отклика, функциональная система дыхания, имитация течения инфекционного заболевания, интегрированная математическая модель, взаимодействие функциональных систем организма.