UDC 51-76
DOI: 10.21668/health.risk/2017.4.13.eng

MATHEMATICAL MODEL FOR DESCRIBING ANTI-VIRUS IMMUNE RESPONSE REGULATION ALLOWING FOR FUNCTIONAL DISORDERS IN A BODY*

P.V. Trusov[1, 2], N.V. Zaitseva[1], V.M. Chigvintsev[1, 2], D.V. Lanin[1, 3]

[1]Federal Scientific Center for Medical and Preventive Health Risk Management Technologies, 82 Monastyrskaya Str., Perm, 614045, Russian Federation
[2]Perm National Research Polytechnic University, 29 Komsomolskiy avenue, Perm, 614990, Russian Federation
[3]Perm State University, 15 Bukireva Str., Perm, 614990, Russian Federation

Our task was to create a mathematical model which could describe anti-virus immune response regulation allowing for disorders in the adaptation (neuroendocrine and immune) systems caused by chemical factors of various genesis. We analyzed immune response allowing for immunity types (inborn and acquired one) with certain quantitative parameters chosen in order to characterize them, notably: interferon and NK-cells for inborn immunity, and virus-specific cytotoxic T-cells and antibodies-forming B-lymphocytes for acquired immunity. Regulatory mechanisms incorporated in the model comprise influences exerted by hypothalamus-hypophysis-adrenals system hormones (corticoliberin, adrenocorticotropic hormone, and hydrocortisone), and cytokines (interleukin-1 and interleukin-2) produced by various regulatory cells of the immune system. The suggested model also takes spatial organization of infection and immune processes in different organs and tissues into account as we introduced a time lag for components interaction into it.

The model includes a system of 18 ordinary differential equations with a retarded argument; its parameters characterize how fast various processes influencing an infection dynamics evolve in a body. The parameters are identified on the basis of published experimental data which describe a process of a body being infected with a virus. We calculated dynamics in the immune and neuroendocrine system parameters under a virus infection allowing for disorders in the marrow synthetic function. The model is developed within the framework of a concept viewing a human body as a multi-level model allowing for interactions between its systems and functional state of examined organs under influences exerted on them by hazardous factors of different genesis. The performed research gives a qualitative idea on biological factors which explain an infectious agent kinetics under a virus infection and impacts exerted by factors of various genesis. The results can be applied for adjusting parameters of existing population models, spread and clinical course of various infections, and for making long-term forecasts on an epidemiologic situation which is necessary when we analyze infectious diseases risks, including those which occur under impacts exerted on a human body by hazardous environmental factors.

Key words: *mathematical model, dynamic system, virus disease, inborn immunity, acquired immunity, neuroendocrine regulation.*

Nowadays an issue of describing interrelations in adaptive systems which change their functioning in order to preserve their optimal state under changing conditions is

Petr V. Trusov – Doctor of Physical and Mathematical Sciences, Professor, Head of Mathematic Modeling of Systems and Processes Department, Chief Researcher (e-mail: tpv@matmod.pstu.ac.ru, tel.: +7 (342) 239-16-07).

Nina V. Zaitseva – Member of the Russian Academy of Sciences, Doctor of Medical Sciences, Professor, Director (e-mail: znv@fcrisk.ru; tel.: +7 (342) 237-25-34).

Dmitrii V. Lanin – Doctor of Medical Sciences, Associate Professor, Leading Researcher at Immune Biological Diagnostic Techniques Department, Professor at Human Ecology and Life Safety Department (e-mail: dmlan@fcrisk.ru; tel.: +7 (342) 237-18-04).

Vladimir M. Chigvintsev – Researcher at Mathematic Modeling of Systems and Processes Department, post-graduate student at Mathematic Modeling of Systems and Processes Department (e-mail: cvm@fcrisk.ru; tel.: +7 (342) 237-18-04).

* The research was performed duevti funancial support by RFBR within the scientific project No 16-31-00333 mol_a.

of great interest to researchers both in the sphere of neuroendocrine regulation and immune mechanisms [25, 30]. Works published in the field focus on various sings of mutual regulatory influences [17, 41]. Some research dwells on neuroendocrine regulation of the immune system [4, 19, 29] and controlling influence exerted by the immune system, for example, via cytokines production, both on itself and on the neuroendocrine regulatory loop [37, 41]. Most experts believe neuroendocrine and immune regulatory loops are a unified "super"-regulatory meta-system [9, 21], which coordinates a complicated multi-level controlling process in a living system. The immune system is responsible for various mechanisms aimed at a macro-organism protection, including those preventing from virus infections. Losses occurring due to infectious morbidity make a considerable contribution into overall damages done to population by various health disorders and are a great medical and social problem [44]. Thus, morbidity with children virus infections (measles, chicken pox, and rubella) is significant among children population [12]. Acute respiratory virus infections in the RF take the first place among reasons for a temporary disability among adult population. Increased morbidity with virus hepatitis [11], HIV-infection [1], etc. is another serious problem.

Technogenic environmental factors can cause pathomorphism and lead to deterioration of infectious diseases clinical course and outcome [8,10,12,13]. Technogenic processes exert influence on regulatory (immune and neuroendocrine) systems; thus, for example, it was shown [3], that technogenic chemical factors exerted negative impacts on the said systems functioning.

Observation techniques or an experimental approach which are conventionally applied in biology and medicine to assess functional disorders in the immune and neuroendocrine system usually involve consequent statistical processing of the results. In spite of all their significance, they don't fully allow to analyze mechanisms and assess consequences caused by an effect occurring when functional disorders accumulate in body systems. It is due to limitations which exist in choice of representative groups, complications related to identification and detection of basic factors, and substantial material costs which are required for organizing and conducting experiments.

Mathematical modeling seems to be one of the most efficient approaches to finding an optimal strategy for examining as well as predicting clinical course of virus diseases. To study regulatory systems influences, we previously suggested to apply a mathematical model of interaction between the immune and neuroendocrine system which we developed on the example of a bacterial infection [14]. This approach allows to save time and resources required for solving the set tasks. Mathematical models make it possible to analyze influence exerted by various factors and their combinations on an individual and population level. An example of such models is mathematical prediction models which describe correlation between human health and environmental factors [7].

Our research goal was to give a mathematical description of an interaction between the immune and neuroendocrine systems mechanisms which occurs under a virus infection; this description allowed for functional disorders caused by negative influences exerted by chemical environmental factors.

Data and methods. Structural scheme of our model given in Figure 1 is a set of interrelated immune and neuroendocrine system elements which are the most significant components in a body response to a virus invasion. The model allows for func-

tional state of organs which are being considered. We can highlight such factors influencing changes in their state as natural ageing and negative impacts exerted by various chemicals penetrating a body from the environment.

As we describe interactions between the immune and endocrine system which are very complicated we introduce certain simplifying assumptions into the design of our model. Cells and viruses populations are assumed to be evenly spread over the epithelial layer of a target organ at any moment. We also assume that speed of changes in any variable in the model is determined by the current values of all the variables. At present we assume that the basic processes which regulate immune protection dynamics take place in three local volumes: brains (hypophysis and hypothalamus), abdominal cavity (adrenals), and a target organ. Interaction between these three local volumes occurs with a time lag.

Protection mechanisms are activated after macrophages have started interaction with dead cells of a target organ which were destroyed due to a virus life cycle. As macrophages remove cells damaged by a virus, simultaneously information molecules of (cytokine) interleukin-1 are synthesized [22].

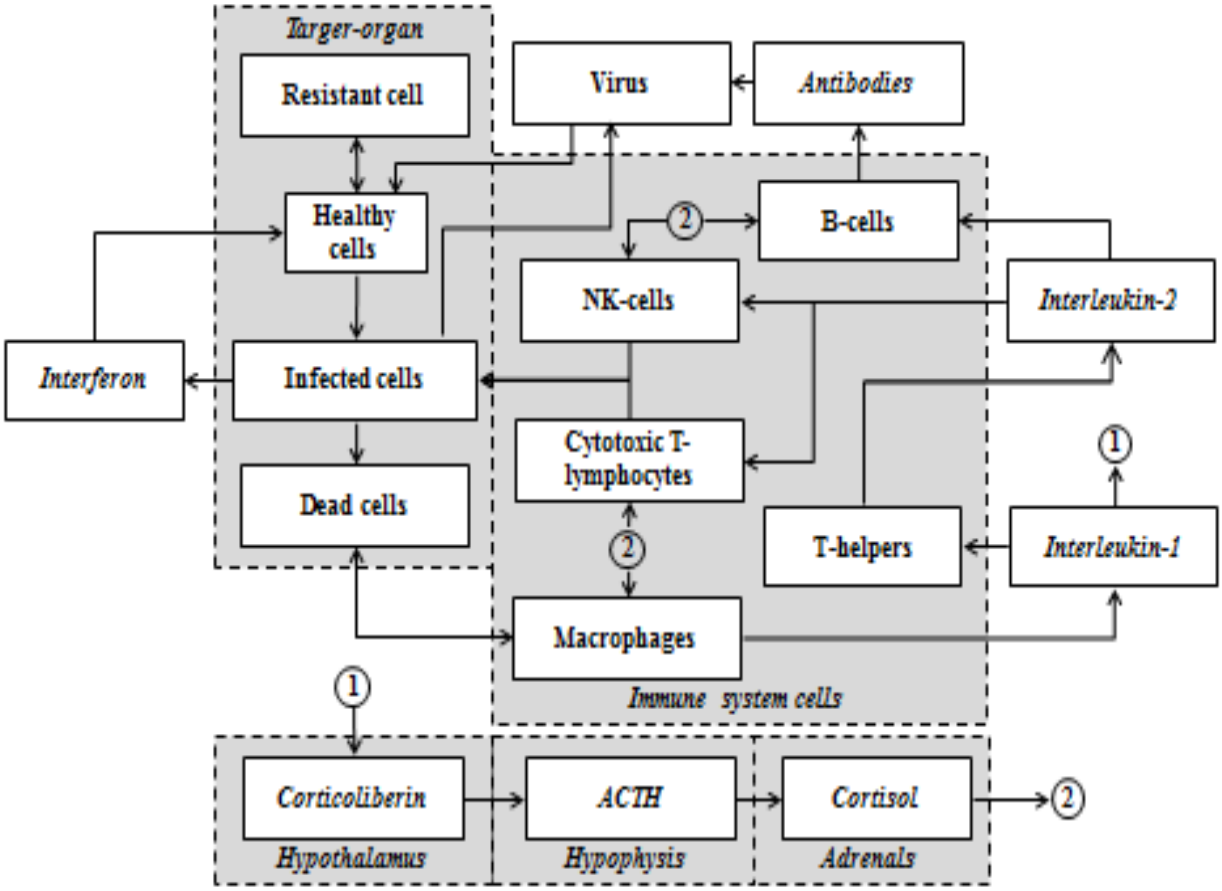


Figure 1. Immune and neuroendocrine system functioning in case virus infection occurs: a conceptual scheme

As interleukin-1 concentration in blood increases, it makes for T-helpers producing interleukin-2 and stimulates specific receptors in the hypothalamus to produce corticoliberin, a release hormone. Corticoliberin influences the adenohypophysis and causes adrenocorticotropic hormone (ACTH) secretion [18], When penetrating blood, ACTH stimulates the adrenals to produce hydrocortisone; increased concentration of this hormone inhibits ACTH secretions and blocks interleukin-1 production as per negative feedback mechanism.

Regulatory impacts exerted by interleukin-2 are aimed at NK-cells cytotoxic T-lymphocytes and B-cells [15, 32, 35]. Basic NK-cells function is related to infected cells elimination at early stages of a body protecting against virus infections. NK-cells are produced by the marrow. NK-cells activity is influenced by various cytokines and hormones produced by a body. In our work we allow for inhibiting effects exerted by hydrocortisone and stimulating influence by interleukin-2 [24, 28, 36].

Infected cells produce interferon and it is another mechanism of primary anti-virus body protection [31, 39, 40]. Interferon influences neighboring uninfected cells and invokes resistance to virus infection in them [20]. This resistance is temporary and then cells transfer into adiaphoria thus becoming resistant to interferon influence for a while [33]. There are basic mechanisms of specific acquired immune response: B-cells produce antibodies [16], which bind free viruses, and cytotoxic T-lymphocytes destroy cells infected with viruses [36]. Active reproduction of the above-mentioned immune response cells starts after a body gives its first signals that a virus infection has occurred; these signals are given via stimulating effects by interleukin-2. Activation of antibodies production by B-cells and T-killers entering the circulatory and lymphatic systems occurs only when a number of specific cells reaches a certain level. Hydrocortisone inhibits antiviral activity of the examined cells. The initial number of acquired immune response cells depends on the marrow functional state and previous case history of a body being infected with this virus.

Basing on the above-given interaction scheme we can describe a mathematical model of the regulation mechanism comprising elements of the immune and endocrine system with the help of the designed model which is a system consisting of 18 ordinary first-order differential equations with a retarded argument (1):

$$
\begin{cases}
\dfrac{dC_{HE}}{dt} = k_1\left(C_{HE}+C_R\right)C_D + k_2 C_R - k_3 C_{HE} C_{IFN} - k_4 C_{HE} C_V \\
\dfrac{dC_I}{dt} = k_4 C_{HE} C_V - k_5 C_{NK} C_I C_{IL2}\left(1 - k_8 \dfrac{C_K\left(t-T\right)}{\mathrm{k}_{47} + C_K\left(t-T\right)}\right) - \\
-k_6 C_{CTL} C_I \left(1 - k_9 \dfrac{C_K\left(t-T\right)}{\mathrm{k}_{47} + C_K\left(t-T\right)}\right) H\left(C_{CTL} - k_{46}\right) - k_7 C_I \\
\dfrac{dC_R}{dt} = k_3 C_{HE} C_{IFN} - k_2 C_R \\
\dfrac{dC_{IFN}}{dt} = k_{10} C_I - k_{11} C_{HE} C_{IFN} - k_{12} C_{IFN} \\
\dfrac{dC_D}{dt} = k_7 C_I + k_5 C_{NK} C_I C_{IL2}\left(1 - k_8 \dfrac{C_K\left(t-T\right)}{\mathrm{k}_{47} + C_K\left(t-T_2\right)}\right) + \\
+k_6 C_{CTL} C_I \left(1 - k_9 \dfrac{C_K\left(t-T\right)}{\mathrm{k}_{47} + C_K\left(t-T\right)}\right) H\left(C_{CTL} - k_{46}\right) - k_{13} C_D C_M \\
\dfrac{dC_V}{dt} = k_{14} C_I - k_{15} C_V C_A - k_{16} C_V C_{HE} - k_{17} C_V \\
\dfrac{dC_M}{dt} = k_{18} F_b - k_{19} C_M \\
\dfrac{dC_{IL1}}{dt} = k_{20} C_M C_D \left(1 - k_{21} \dfrac{C_K\left(t-T\right)}{\mathrm{k}_{47} + C_K\left(t-T\right)}\right) - k_{22} C_{IL1} \\
\dfrac{dC_{TH}}{dt} = k_{23} F_b - k_{24} C_{TH} \\
\dfrac{dC_{IL2}}{dt} = k_{25} C_{TH} C_{IL1} - k_{26} C_{IL2} \\
\dfrac{dC_{NK}}{dt} = k_{27} F_b - k_{28} C_{NK} \\
\dfrac{dC_{CTL}}{dt} = k_{29} + k_{30} C_{CTL} C_{IL2} - k_{32} C_{CTL} - k_{31} C_{CTL} C_I \left(1 - k_9 \dfrac{C_K\left(t-T\right)}{\mathrm{k}_{47} + C_K\left(t-T\right)}\right) H\left(C_{CTL} - k_{46}\right) \\
\dfrac{dC_B}{dt} = k_{46} + k_{33} C_B C_{IL2} - k_{34} C_B \\
\dfrac{dC_A}{dt} = k_{35} C_B \left(1 - k_{36} \dfrac{C_K\left(t-T\right)}{\mathrm{k}_{47} + C_K\left(t-T\right)}\right) H\left(C_B - k_{45}\right) - k_{37} C_V C_A - k_{38} C_A \\
\dfrac{dC_{CRH}}{dt} = \mathrm{k}_{48} F_h \left(1 - k_{39} \dfrac{C_K\left(t-T\right)}{\mathrm{k}_{47} + C_K\left(t-T\right)}\right)\left(1 + k_{40} C_{IL1}\right) - k_{41} C_{CRH} \\
\dfrac{dC_{ACTH}}{dt} = \mathrm{k}_{49} F_p \left(1 - k_{42} \dfrac{C_K\left(t-T\right)}{\mathrm{k}_{47} + C_K\left(t-T\right)}\right) C_{CRH} - k_{43} C_{ACTH} \\
\dfrac{dC_K}{dt} = \mathrm{k}_{50} F_a C_{ACTH}\left(t-T\right) - k_{44} C_K
\end{cases}
\tag{1}
$$

were C_A – antibodies concentration, [mIU/ml];

C_{ACTH} – is adrenocorticotropic hormone (ACTH) concentration, [picogram/ml (pg/ml)];

C_B – is B-cells concentration, [cells/ml];

C_{CTL} – is cytotoxic T-lymphocytes concentration, [cells/ml];

C_{CRH} – is corticoliberin concentration, [pg/ml];

C_D – is number of dead cells in a target organ, [cells];

C_{HE} – is number of healthy cells in a target organ, [cells];

C_I – is number of infected cells in a target organ, [cells];

C_{IL1} – is interleukin-1 concentration, [pg/ml];

C_{IL2} – is interleukin-2 concentration, [pg/ml];

C_{IFN} – is interferon concentration, [ME/ml];

C_K – is hydrocortisone concentration, [nanogram/ml];

C_M – is macrophages (monocytes) concentration, [cells/ml];

C_{NK} – is NK-cells (natural killers) concentration, [cells/ml];

C_R – is number of resistant cells in a target organ, [cells];

C_{TH} – is T-helpers concentration, [cells/ml];

C_V – is antigens concentrations, [copies/ml];

F_a – is adrenals functional capacity, synthesizing function, [dimensionless value];

F_b – is marrow functional capacity, synthesizing function, [dimensionless value];

F_h – is hypothalamus functional capacity, synthesizing function, [dimensionless value];

F_p – is hypophysis functional capacity, synthesizing function, [dimensionless value].

The model parameters were indentified on the basis of experimental data obtained during research on a process of a body being infected with a flu virus; parameters values are given in Table.

We suggest to consider functional disorders in the immune system on the example of the marrow which produces immunocytes. Functional changes in the marrow occurring due to various reasons, chemical contamination included, influence rates at which various inborn and acquired immunity cells are produced. In future it leads both to quantitative (immunocytes and auxiliary immune system cells number dynamics) and qualitative (lower functional activity of immune-competent and auxiliary cells) changes in the immunity, including those evolving due to autoregulation mechanisms disorders. Functional disorders in the neuroendocrine system elements which we described earlier and which can be caused by chemical environmental factors [3, 5], in their turn, are able to result in the "outer" immune system failure and lower immune response efficiency.

To describe this factor, we apply a mathematical model which allows to predict functional disorders evolution under exposure to environmental factors. The model allows for body age-related peculiarities, and functional disorders accumulation due to natural processes occurring in a body and environmental factors impacts.

Disorders in each organ's functional abilities is characterized with a functional damage parameter . ; means an organ functions properly (perfectly). means an organ is unable to fulfill its functions.

Parameters of the mathematical model describing interactions between the immune and endocrine systems under a virus infection

Parameter	Value	Source	Parameter	Value	Source
k_1	$2.35*10^{-11}$ [1/cells*day]	[34]	k_{27}	$1.1*10^{14}$ [cells/ml*day]	
k_2	0.98 [1/day]	[36]	k_{28}	0.11 [1/day]	
k_3	$1.1*10^{-17}$ [ml/IU*day]	[21]	k_{29}	$4*10^{15}$ [cells/ml*day]	[36]
k_4	$2*10^{-12}$ [ml/copies*day]	[36]	k_{30}	4.15 [ml/pg*day]	[36]
k_5	$2.5*10^{-17}$ [ml^2/cells*pg*day]		k_{31}	$1.6*10^{-11}$ [1/ cells*day]	[21]
k_6	$6.6*10^{-18}$ [ml/pg*day]	[21]	k_{32}	0.4 [1/day]	[36]
k_7	1.5 [1/day]	[2]	k_{33}	5.75 [ml/pg*day]	[36]
k_8	0.5 [dimensionless]		k_{34}	0.4 [1/day]	[36]
k_9	0.5 [dimensionless]		k_{35}	$7.56*10^{12}$[mIU/cells]	[36]
k_{10}	$3.2*10^{6}$ [IU/cells*ml*day]		k_{36}	0.5 [dimensionless]	
k_{11}	$1.01*10^{-10}$ [1/cells*day]	[21]	k_{37}	$8.6*10^{-10}$ [ml/copies*day]	[21]
k_{12}	8 [1/day]	[21]	k_{38}	0.043 [1/day]	[36]
k_{13}	10^{-14} [ml/cells*day]		k_{39}	0.5 [dimensionless]	
k_{14}	510 [copies/ml*cells*day]	[2]	k_{40}	0.002 [ml/pg]	
k_{15}	$8.6*10^{-10}$ [ml/mIU*day]	[43]	k_{41}	3.767 [1/day]	[26]
k_{16}	$6.1*10^{-12}$ [1/cells*day]	[21]	k_{42}	0.5 [dimensionless]	
k_{17}	1.7 [1/day]	[21]	k_{43}	0.7572 [1/day]	[38]
k_{18}	$3*10^{9}$ [cells/ml*day]	[36]	k_{44}	0.1972 [1/day]	[38]
k_{19}	0.03 [1/day]	[36]	k_{45}	$1.8139*10^{20}$ [cells/ml]	
k_{20}	$2.94*10^{-19}$ [pg/$cells^2$*day]	[20]	k_{46}	$0.4*10^{16}$ [cells/ml]	[36]
k_{21}	0.5 [dimensionless]		k_{47}	3.055 [ng/ml]	[42]
k_{22}	0.1245 [1/day]	[27]	k_{48}	7.659 [pg/ml]	[26]
k_{23}	$5.8*10^{3}$[cells/ml*day]		k_{49}	21 [pg/ml]	[38]
k_{24}	0.0058 [1/day]		k_{50}	3.055 [ng/ml]	[42]
k_{25}	$3.28*10^{-7}$ [ml/cells*day]		T	0.0132 [day]	[42]
k_{26}	0.248 [1/day]			$1.1*10^{14}$ [cells/ml*day]	

Outer (for an organ being considered) impacts and internal degradation (ageing) are basic reasons for damages in it. Outer impacts are hazardous substances penetrating into a body and influencing damages to an organ.

Assuming that damages speeds depend on various factors, we suggest the following structure of equations describing evolution of functional damages to human organs (2):

$$\frac{dF}{dt} = \alpha F + \sum_{i=1}^{n} \beta_i \left\langle \frac{p_i}{p_i^N} - 1 \right\rangle, \qquad (2)$$

where α – is a coefficient which characterizes a speed at which an organ grows older [1/year];

β_i – is a coefficient which characterizes a value of impacts exerted by i-th hazardous factors on functional damages to an organ [1/year];

p_i – is i-th hazardous substance introduction into a human body;

p_i^N – is standard (maximum permissible) value of i-th substance introduction for an organ being considered.

So called McCauley brackets are given as $\langle x \rangle$ будут обозначаться так называемые скобки Мак-Кейли (McCauley): $\langle x \rangle = 0$ при $x < 0$ и $\langle x \rangle = x$ при $x \geq 0$.

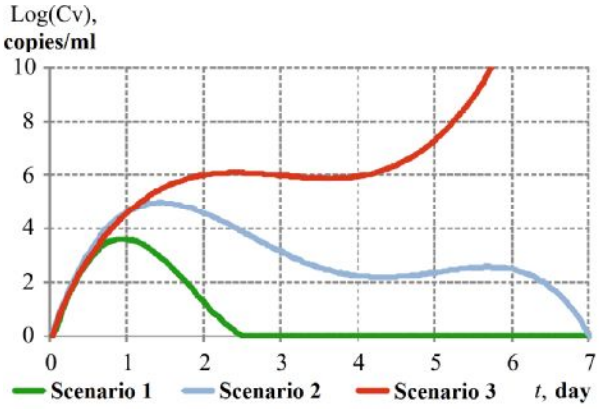
The first summand in the equation (2) makes an additional contribution into functional damages due to an increase in the intensity an undamaged part of an organ functions with in case any structural damages disorders occur; this increased intensity results from the necessity for a healthy part of an organ to enter an enhanced mode required for proper organ functioning. This enhanced functioning mode decreases cells life and causes faster organ destruction.

The second summand characterizes damages caused by environmental factors which can occur due to excessive hazardous substances introduction. The suggested structure describes the overall picture of damages evolution and allows for self-destruction (natural ageing) and damages accumulation caused by hazardous substances introduction which is beyond the set standards.

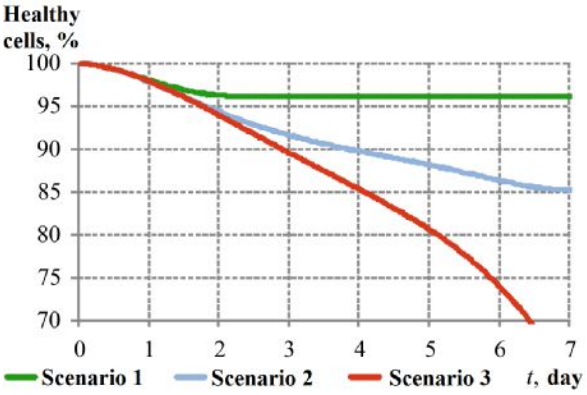
As all the equations in the model are complicated and non-linear, it becomes more difficult to obtain analytical solution with its application. To solve the differential equation system, we apply implicit numerical technique by Runge-Kutta of the third order.

Results and discussion. To test our model, we performed a numerical experiment and implemented three possible scenarios of the system behavior. The difference between them was related to the degree of disorders in the marrow synthesizing function, and this degree was determined by the intensity of impacts exerted by negative chemical factors. Each scenario involved breaking the system balance by setting up the initial viruses level. The results are given in Figures 2.

Our first scenario modeled virus invasion and a body successful fighting against it ($F_b = 1$). Initially macrophages produced interleukin-1 which stimulated interleukin-2 production. The latter in its turn activated NK-cells which were already present in a body; they rapidly inhibited infected cells thus preventing viruses from being released. After all viruses were successfully destroyed, interleukin-1 concentration went down to zero. Tentatively speaking, we can assume that it will correspond either to absence of any clinical signs of a disease or to a very mild form of it which will result in complete and fast recovery.



a



b

Figure. 2. *a* – Graph showing changes in number of virus copies in a body over time and depending on damages to the marrow synthesizing function Graph showing changes in number of virus copies in a body over time and depending on damages to the marrow synthesizing function; *b* – Graph showing changes in % of healthy cells quantity against their initial level

The second scenario describes activation of not only inborn immunity but also acquired one ($F_b = 0{,}85$). If we take clinical practices, a disease with average gravity can be an example of such a scenario. At initial stages fighting against a virus is based on inborn immunity. But a body can't overcome it and viruses continue to reproduce themselves. Acquired immunity activations occurs on the fifth day and a number of viruses goes down rapidly. We can observe this scenario when the marrow

synthesizing function is a bit weakened, when virus load is substantial, or when there is no immune memory about this concrete type of viruses.

The third scenario concentrates on virus invasion in case when the marrow synthesizing function is significantly reduced ($F_b = 0{,}7$) as a result of adverse impacts exerted by the environment. These impacts cause initially low levels of macrophages, NK-cells, B-cells, and cytotoxic T-lymphocytes in a body. As a result a number of viruses in a body grows continuously. It can correspond to a very serious disease or even lethal outcome of it.

When an infection occurs, a number of healthy cells in a target organ gradually goes down due to negative impacts exerted by viruses. There are the following gradations for damages to a target organ tissue corresponding to a disease clinical form: damage to less than 8-10% of a tissue corresponds to a mild disease; 10-20%, an average disease; 20-25%, a grave disease; when more than 25-30% of a target organ tissue is damaged, lethal outcome is rather probable [6].

Conclusions. So, the suggested predictive mathematical model of regulatory systems functioning under virus invasion and under exposure to chemical factors represents the occurring processes quite qualitatively and sufficiently. This model is a simplified variant of a complicated multi-component process of interaction between regulatory systems under chemical contamination when virus invasion occurs. However, it allows to show mechanics of multi-component interaction between regulatory systems when inflammatory reactions of viral genesis evolve. Basing on it, in future we plan to expand the model component structure possibly performing population analysis of dependence between infectious morbidity and chemical contamination.

References

1. Voronin E.E., Latysheva I.B. VICh-infektsiya v Rossiiskoi Federatsii [HIV in the Russian Federation]. *Ural'skii meditsinskii zhurnal*, 2016, no. 9 (142), pp. 6–8 (in Russian).

2. Zhdanov V.M., Bukrinskaya A.G. Reproduktsiya miksovirusov (virusov grippa i skhodnykh s nimi) [Mixoviruses reproduction (influenza viruses and those similar to them)]. Moscow, Meditsina, Publ., 1969, 280 p. (in Russian).

3. Zaitseva N.V., Lanin D.V., Chereshnev V.A. Immunnaya i neiroendokrinnaya regulyatsiya v usloviyakh vozdeistviya khimicheskikh faktorov razlichnogo geneza [Immune and neuroendocrine regulation under exposure to chemical factors of various genesis]. Perm', Izdatel'stvo Permskogo natsional'nogo issledovatel'skogo politekhnicheskogo universiteta, Publ., 2016, 236 p. (in Russian).

4. Lanin D.V., Zaitseva N.V., Dolgikh O.V. Neiroendokrinnye mekhanizmy regulyatsii funktsii immunnoi sistemy [Neuroendocrine Mechanisms for Regulation of Immune System]. *Uspekhi sovremennoi biologii*, 2011, no. 2, pp. 122–134 (in Russian).

5. Lanin D.V., Lebedeva T.M. Vozdeistvie khimicheskikh faktorov sredy obitaniya na funktsii i vzaimosvyazi regulyatornykh sistem u detei [The influence of chemical environmental factors on functions and interrelationships of regulatory systems in children]. *Gigiena i sanitariya*, 2016, vol. 95, no. 1, pp. 94–96 (in Russian).

6. Marchuk G.I., Berbentsova E.P. Ostrye pnevmonii. Immunologiya, otsenka tyazhesti, klinika, lechenie [Acute pneumonias. Immunology, gravity assessment, clinical course, and treatment]. Moscow, Nauka,Publ., 1989, 304 p. (in Russian).

7. Zaitseva N.V., Shur P.Z., May I.V., Kiryanov D.A. Metodicheskie podkhody k otsenke integral'nogo riska zdorov'yu naseleniya na osnove evolyutsionnykh matematicheskikh modelei [Approaches to the assessment of integrated health risk population based on evolution of mathematical models]. *Zdorov'e naseleniya i sreda obitaniya*, 2011, no. 10, pp. 6–9 (in Russian).

8. Stepanenko L.A., Savchenkov M.F., Il'ina S.V., Anganova E.V., Savilov E.D. Otsenka sostoyaniya immunnoi sistemy detskogo naseleniya kak markera tekhnogennogo zagryazneniya okruzhayushchei sredy [An assessment of the immune status of the children population as a marker of technogenic pollution of the environment]. *Gigiena i sanitariya*, 2016, vol. 95, no.12, pp. 1129–1133 (in Russian).

9. Poletaev A.B., Morozov S.G., Kovalev I.E. Regulyatornaya metasistema (immunoneiroendokrinnaya regulyatsiya gomeostaza) [Regulatory meta-system (immune-neuroendocrine homeostasis regulation)]. Moscow, Meditsina, Publ., 2002, 166 p. (in Russian).

10. Savilov E.D., Il'ina S.V. Osobennosti infektsionnoi patologii detskogo naseleniya v usloviyakh tekhnogennogo zagryazneniya okruzhayushchei sredy [Features of Infectious Pathology in the Child Population in the Conditions of Technogenic Pollution of the Environment]. *Epidemiologiya i vaktsinoprofilaktika*, 2012, no. 1 (62), pp. 58–63 (in Russian).

11. Savilov E.D., Mal'tsev M.V. Epidemiologicheskaya kharakteristika virusnogo gepatita S v usloviyakh krupnogo promyshlennogo goroda [Epidemiological characteristic of viral hepatitis c in large industrial city settings]. *Zhurnal mikrobiologii, epidemiologii i immunobiologii*, 2007, no. 1, pp. 70–71 (in Russian).

12. Stepanenko L.A., Il'ina S.V., Savilov E.D. Osobennosti sostoyaniya spetsificheskogo immuniteta k upravlyaemym infektsiyam u detei (na primere kori i poliomielita) v usloviyakh vozdeistviya tekhnogennoi nagruzki [Peculiarities of specific immunity to manageable infections in children (on the examples of measles and polyomielitis) under impacts exerted by technogenic loads]. *Byulleten' Vostochno-Sibirskogo nauchnogo tsentra Sibirskogo otdeleniya Rossiiskoi akademii meditsinskikh nauk*, 2007, no. S3, pp. 66–68 (in Russian).

13. Savilov E.D., Anganova E.V., Il'ina S.V., Stepanenko L.A. Tekhnogennoe zagryaznenie okruzhayushchei sredy i zdorov'e naseleniya: analiz situatsii i prognoz [Technogenic environmental pollution and the public health: analysis and prognosis]. *Gigiena i sanitariya*, 2016, vol. 95, no. 6, pp. 507–512 (in Russian).

14. Zaitseva N.V., Kiryanov D.A., Lanin D.V., Chigvintsev V.M. A mathematical model of the immune and neuroendocrine systems mutual regulation under the technogenic chemical factors impact. *Computational and Mathematical Methods in Medicine*, 2014. Available at: https://www.hindawi.com/journals/cmmm/2014/492489/abs/ (18.04.2017)

15. Andrew M.E., Churilla A.M., Malek T.R., Braciale V.L., Braciale T.J. Activation of virus specific CTL clones: antigen-dependent regulation of interleukin 2 receptor expression. *J Immunol*, 1985, no. 134 (2), pp. 920–925.

16. Tamura S.I., Iwasaki T., Thompson A.H., Asanuma H., Chen Z., Suzuki Y., Aizawa C., Kurata T. Antibody-forming cells in the nasal-associated lymphoid tissue during primary influenza virus infection. *Journal of General Virology*, 1998, vol.79, no. 2, pp. 291–299.

17. Ashley N.T., Demas G.E. Neuroendocrine-immune circuits, phenotypes, and interactions. *Hormones and Behavior*, 2017, vol. 87, pp. 25–34.

18. Bairagi N., Chatterjee S., Chattopadhyay J. Variability in the secretion of corticotropin-releasing hormone, adrenocorticotropic hormone and cortisol and understandability of the hypothalamic-pituitary-adrenal axis dynamics – a mathematical study based on clinical evidence. *Mathematical Medicine and Biology*, 2008, vol. 25, no. 1, pp. 37–63.

19. Bellavance M., Rivest S. The neuroendocrine control of the innate immune system in health and brain diseases. *Immunological Reviews*, 2012, vol. 248, no. 1, pp. 36–55.

20. Bocharov G.A., Romanyukha A.A. Mathematical model of antiviral immune response III. Influenza A virus infection. *Journal of Theoretical Biology*, 1994, vol. 167, no. 4, pp. 323–360.

21. Chapman C.R., Tuckett R.P., Song C.W. Pain and Stress in a Systems Perspective: Reciprocal Neural, Endocrine, and Immune Interactions. *Journal of Pain*, 2008, vol. 9, no. 2, pp. 122–145.

22. Zabel P., Horst H.J., Kreiker C., Schlaak M. Circadian rhythm of interleukin-1 production of monocytes and the influence of endogenous and exogenous glucocorticoids in man. *Klinische Wochenschrift*, 1990, vol. 68, no. 24, pp. 1217–1221.

23. Bergeron Y., Ouellet N., Deslauriers A., Simard M., Olivier M., Bergeron M. Cytokine kinetics and other host factors in response to pneumococcal pulmonary infection in mice. *Infect. Immun*, 1998, vol. 66, no. 3, pp. 912–922.

24. Demas G.E., Adamo S.A., French S.S. Neuroendocrine-immune crosstalk in vertebrates and invertebrates: Implications for host defence. *Functional Ecology*, 2011, vol. 25, no. 1, pp. 29–39.

25. Pace T.W., Negi L.T., Adame D.D., Cole S.P., Sivilli T.I., Brown T.D., Issa M.J., Raison C.L. Effect of compassion meditation on neuroendocrine, innate immune and behavioral responses to psychosocial stress. *Psychoneuroendocrinology*, 2009, no. 34, pp. 87–98.

26. Felig P., Frohman L. Endocrinology and metabolism, 4er ed. New York, McGraw-Hill, Publ., 2001, 1562 p.

27. Gloff C., Wills R. Pharmacokinetics and Metabolism of Therapeutic Cytokines. In B. Ferraiolo, M. Mohler, C. Gloff, eds. New York, Plenum Press, Publ., 1992, pp. 127–150.

28. Haus E., Smolensky M.H. Biologic rhythms in the immune system. *Chronobiology international*, 1999, vol. 16, no. 5, pp. 581–622.

29. Heffner K.L. Neuroendocrine Effects of Stress on Immunity in the Elderly: Implications for Inflammatory Disease. *Immunology and Allergy Clinics of North America*, 2011, vol. 31, no. 1, pp. 95–108.

30. Heijnen C.J. Receptor regulation in neuroendocrine-immune communication: current knowledge and future perspectives. *Brain, behavior, and immunity*, 2007, vol. 21, no. 1, pp. 1–8.

31. Julkunen I., Melen K., Nyqvist M., Pirhonen J., Sareneva T., Matikainen S. Inflammatory responses in influenza A virus infection. *Vaccine*, 2000, vol. 19, no. 1, pp. 32–37.

32. Muraguchi A., Kehrl J.H., Longo D.L., Volkman D.J., Smith K.A., Fauci A.S. Interleukin 2 receptors on human B cells. Implications for the role of interleukin 2 in human B cell function. *The Journal of experimental medicine*, 1985, vol. 161, no. 1, pp. 181–97.

33. Joklik W.K. Interferons. In: B.N. Fields, ed. New York, Raven Press, Publ., 1985, pp. 281–307.

34. Keenan K.P., Combs J.W., McDowell E.M. Regeneration of hamster tracheal epithelium after mechanical injury. *Virchows Archiv B Cell Pathology Including Molecular Pathology*, 1983, vol. 42, no. 1, pp. 231–252.

35. Kerdiles Y., Ugolini S., Vivier E. T cell regulation of natural killer cells. *The Journal of Experimental Medicine*, 2013, vol. 210, no. 6, pp. 1065–1068.

36. 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. *Journal of Theoretical Biology*, 1991, vol. 151, no. 1, pp. 1–40.

37. Miyake S. Mind over cytokines: Crosstalk and regulation between the neuroendocrine and immune systems. *Clinical and Experimental Neuroimmunology*, 2012, vol. 3, no. 1, pp. 1–15.

38. Carroll B.J., Cassidy F., Naftolowitz D., Tatham N.E., Wilson W.H., Iranmanesh A., Liu P.Y., Veldhuis J.D. Pathophysiology of hypercortisolism in depression. *Acta Psychiatrica Scandinavica*, 2007, vol. 115, pp. 90–103.

39. Ronni T., Sareneva T., Pirhonen J., Julkunen I. Activation of IFN-alpha, IFN-gamma, MxA, and IFN regulatory factor 1 genes in influenza A virus-infected human peripheral blood mononuclear cells. *Journal of immunology*, 1995, vol. 154, no. 6, pp. 2764–2774.

40. Sareneva T., Matikainen S., Kurimoto M., Julkunen I. Influenza A virus-induced IFN-alpha/beta and IL-18 synergistically enhance IFN-gamma gene expression in human T cells. *Journal of immunology*, 1998, vol. 160, no. 12, pp. 6032–6038.

41. Suarez E.C., Sundy J.S., Erkanli A. Depressogenic vulnerability and gender-specific patterns of neuro-immune dysregulation: What the ratio of cortisol to C-reactive protein can tell us about loss of normal regulatory control. *Brain, Behavior, and Immunity*, 2015, no. 44, pp. 137–147.

42. Vinther F., Andersen M., Ottesen J.T. The minimal model of the hypothalamic-pituitary-adrenal axis. *Journal of Mathematical Biology*, 2011, vol. 63, no. 4, pp. 663–690.

43. Wohlfartt C. Neutralization of Adenoviruses: Kinetics, Stoichiometry, and Mechanisms. *J Immunol*, 1988, vol. 62, no. 7, pp. 2321–2328.

44. World Health Organization World Health Organization. World health statistics 2016: monitoring health for the SDGs, sustainable development goals. *World Health Organization*, 2016, 121 p.

Trusov P.V., Zaitseva N.V., Chigvintsev V.M., Lanin D.V. Mathematical model for describing anti-virus immune response regulation allowing for functional disorders in a body. Health Risk Analysis, 2017, no. 4, pp. 117–128. DOI: 10.21668/health.risk/2017.4.13.eng

Received: 18.08.2017
Accepted: 20.12.2017
Published: 30.12.2017