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========== TRANSLATIONS OF PUBLISHED ARTICLES ==========

Regulation of Organism's Antiviral Immune Response: Mathematical Model, Qualitative Analysis, Results

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Abstract. To know the processes occurring in the neuroendocrine and immune system, the complex and branching regulation mechanisms should be taken into account. Most of the studies in this area are dedicated to the biological and mathematical description of individual parts of the regulatory mechanisms, and it greatly facilitates the understanding of the phenomena being studied. But there is a lack of comprehensive description of the processes and internal communications. In the present article, a mathematical model for describing the antiviral immune response is considered taking into account the interacting regulatory influences of the immune and neuroendocrine systems. To describe the innate immunity, the proposed model uses parameters reflecting quantitative measures of the interferon concentration (the inductor of resistance to the infection of target organ cells) and NK-cells (responsible for removing of the infected cells). The simulation of acquired immunity is performed using parameters characterizing the concentration of virus-specific cytotoxic T cells and antibody-forming B lymphocytes. The regulatory mechanisms considered in the model cover the influence of the hypothalamic-pituitary-adrenal axis and the populations of the T-helper cells. The model is developed within the framework of the concept of a multi-level model of the human body, taking into account the interactions between systems and the functional state of the organs included in the review. The model also takes into account the spatial organization of immune and infectious processes in various organs and tissues, for which the delay time of interaction of the components is introduced. The model includes a system of 18 ordinary differential equations with a delayed argument, the parameters of which characterize the rates of various processes that affect the dynamics of infection. The parameters are identified according to published experimental data describing the process of infection of the body with a virus. The dynamics of the immune and neuroendocrine systems under viral infection was calculated, taking into account the disturbance of the synthetic function of the bone marrow. The study provides a qualitative picture of the biological factors that can explain the kinetics of the development of a viral infection.

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

INTRODUCTION

At present, interrelations between adaptive systems are given a lot of attention by researchers, concerning both neuroendocrine regulation and immune mechanisms [1, 2]. Studies in this area describe regulatory effects [3, 4]; analyze neuroendocrine regulation of the

immune system [5, 6] and managing influence exerted by it both on itself and the neuroendocrine regulatory loop through, for example, cytokine release [7, 8]. Most experts believe that the neuroendocrine and immune regulatory loops together create a super-regulatory meta-system [7, 9] that coordinates a complex multi-level management process in a live organism. The immune system is responsible for various mechanisms protecting a macro-organism, including those protecting from vital infections. Losses caused by such communicable diseases account for a significant part of damage to a population due to various health disorders and therefore are a serious medical and social issue [10]. Thus, incidence of childhood viral infections is high among children (measles, chicken pox, and rubella) [11]. Acute respiratory infections hold the first place in the RF as a cause of temporal loss of working ability among adults [12]. Another urgent issue is growing incidence of viral hepatitis [13], HIV infection [14] etc.

Technogenic environmental factors can lead to pathomorphosis, aggravate a clinical course and outcome of communicable diseases [15–17]. This process involves regulatory (immune and neuroendocrine) systems; technogenic chemical factors have been reported [18, 19] to have negative effects on functioning of the aforementioned system.

In biology and medicine, observation methods or an experimental approach are conventionally used to assess functional disorders of the immune and neuroendocrine system and assessments are usually followed by statistical analysis of their results. Despite their high significance, these methods and approaches do not provide an opportunity to perform comprehensive analysis and assessment of outcomes caused by functional disorders accumulating in the body. Impossibility to achieve this is caused by certain limitations in selecting representative groups, difficulties in identifying and detecting major influencing factors, and need in considerable material costs to organize and perform experiments.

Mathematical modeling seems to be one of the most effective approaches to developing an optimal strategy for investigating viral infections as well as predicting their clinical course. Previously, we suggested using our mathematical model of interaction between the immune and endocrine system exemplified by a bacterial infection to investigate influence of the regulatory systems [20]. This approach saves time and resources necessary for solving the outlined task. Mathematical models make it possible to analyze effects produced by various factors or their combinations on individual and population levels. Mathematical prediction models that describe relations between health indicators and environmental factors are a relevant example [21, 22].

CONCEPTUAL STATEMENT

This study presents a mathematical model that describes interaction between various mechanisms of the immune and neuroendocrine systems. The model considers functional disorders of organs involving failure to produce (synthesize) relevant substances in an example situation when the analyzed system interact under a viral infection. The structural scheme of the model is shown in Figure 1; it includes a set of interrelated elements of the immune and neuroendocrine systems, the most significant components in a body response to a viral invasion. The model considers functional state of the analyzed organs. Several factors that induce changes in their state include natural ageing and negative effects produced by various chemicals that ether the body from the environment.

We suggest examining functional disorders of the immune system on the example of the bone marrow, an organ that produces immunocytes. Changes in its functioning that can occur, among other things, under chemical contamination influence the speed at which various cells of inborn and acquired immunity are produced. It consequently leads to both quantitative (changes in the number of immunocytes and auxiliary cells of the immune system) and qualitative (lower functional activity of immune-competent and auxiliary cells) changes in immune state, including those occurring due to auto-regulatory mechanisms disorders. In its

turn, functional disorders of the endocrine system components, which we described previously and which can be related to impacts exerted by chemical environmental factors [18, 23], can cause a failure in functioning of the "outer" immune system regulation and decrease in effectiveness of an immune response.

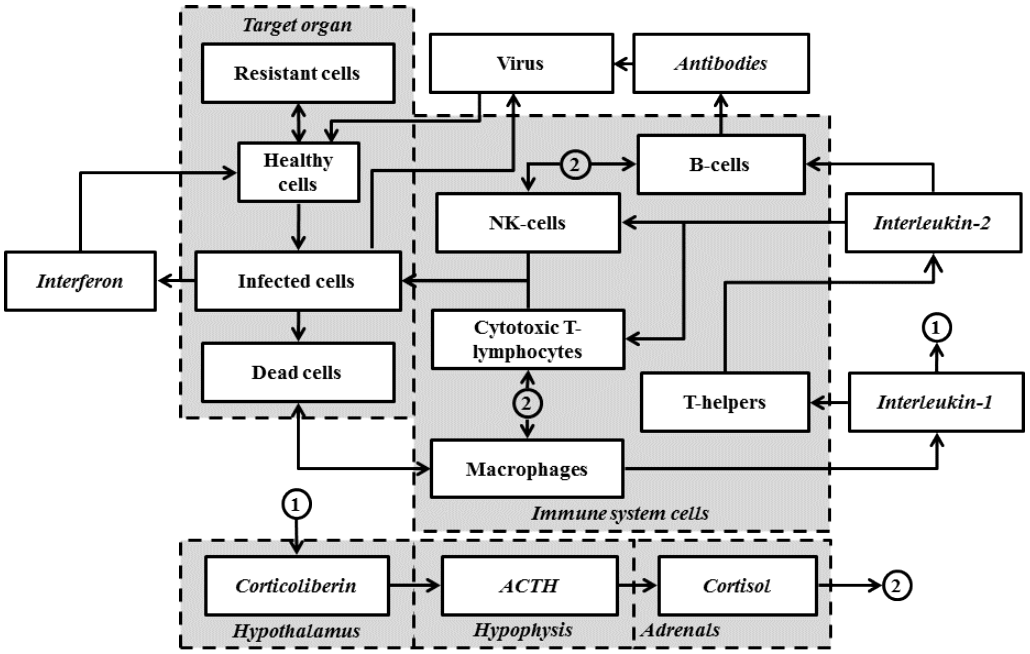

Fig. 1. Functioning of the immune and neuroendocrine systems under a viral invasion.

Since the described interactions between the immune and neuroendocrine systems are rather complicated, we make some simplifying assumptions in this work when creating the model. Cell and virus populations are assumed to be evenly spread over the epithelial layer of a target organ at any moment. We also assume that rate of changes in any variable in the model is determined by the current values of all the variables. In this study, we use a hypothesis that the basic processes regulating immune protection dynamics take place in three local volumes: the brain (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 that were destroyed due to a virus life cycle. As macrophages remove cells damaged by a virus, simultaneously information molecules of interleukin-1 (cytokine) are synthesized [24].

Elevated interleukin-1 levels in blood make for T-helpers producing interleukin-2 and stimulate specific receptors in the hypothalamus to produce corticoliberin, a release hormone. Corticoliberin influences the adenohypophysis and causes adrenocorticotropic hormone (ACTH) secretion [25]. When penetrating blood, ACTH stimulates the adrenals to produce cortisol; increased levels of this hormone inhibit ACTH secretion and block interleukin-1 production as per a negative feedback mechanism.

Elevated interleukin-2 levels stimulate production of NK-cells [26], cytotoxic T-lymphocytes [27], and B-cells [28].

The basic function of NK-cells is to eliminate infected cells at early stages of the body protection against viral infections. NK-cells are produced by the bone marrow. Activity of NK-cells is influenced by various cytokines produced by the body. In our work, we allow for inhibiting effects exerted by cortisol [29, 30] and stimulating influence by interleukin-2 [31].

Infected cells produce interferon and it is another mechanism of primary anti-viral body protection [32]. Interferon influences neighboring uninfected cells and invokes resistance to

virus infection in them (a stable state) [33]. This stable resistance is temporary and then cells become resistant to interferon influence for a while whereas remaining susceptible to viruses.

A specific acquired immune response relies on several mechanisms; that is, B-cells produce antibodies, which bind free viruses, and cytotoxic T-lymphocytes destroy cells infected with viruses [31]. Active reproduction of the above-mentioned immune response cells starts after the body gives its first signals that a viral infection has occurred; these signals are given through stimulating effects by interleukin-2. Production of antibodies by B-cells is activated and T-killers enter the circulatory and lymphatic system only when a number of specific cells reaches a certain level. Cortisol inhibits antiviral activity of the examined cells. The initial number of acquired immune response cells depends on the functional state of the bone marrow and previous cases of the body being infected with this virus.

MATHEMATICAL STATEMENT

Basing on the above-given interaction scheme, we can describe a mathematical model of the regulation mechanism involving elements of the immune and endocrine system. This model is a system consisting of 18 ordinary first-order differential equations with a retarded argument. The model parameters were identified relying on experimental data obtained during examination of a process when the body was infected with influenza virus. It is possible to apply the suggested model to describe an infection caused by another virus but only after additional identification of coefficients that reflect specific features of an examined virus (replication rate and target organ peculiarities).

Table 1. The model variables and scale factors

Variable	Description	Scale factor
C_A	Concentration of antibodies, [mili-international units /ml (mIU/ml)]	$7.2 \cdot 10^{-11}$
C_{ACTH}	Adrenocorticotropic hormone (ACTH) concentration, [picogram/ml (pg/ml)]	3.055
C_B	B-cell concentration, [cells/ml]	$1.8139 \cdot 10^{-20}$
C_{CTL}	Cytotoxic T-lymphocyte concentration, [cells/ml]	10^{-16}
C_{CRH}	Corticoliberin concentration, [pg/ml]	7.659
C_D	Number of dead cells in a target organ, [cells];	$1.7 \cdot 10^{-11}$
F_a	Functional capacity of the adrenals, synthesizing function, [dimensionless value]	1
F_b	Functional capacity of the bone marrow, synthesizing function, [dimensionless value]	1
F_h	Functional capacity of the hypothalamus, synthesizing function, [dimensionless value]	1
F_p	Functional capacity of the hypophysis, synthesizing function, [dimensionless value]	1
C_{HE}	Number of healthy non-resistant cells in a target organ, [dimensionless value]	$1.7 \cdot 10^{-11}$
C_I	Number of infected cells in a target organ, [cells]	$1.7 \cdot 10^{-11}$
C_{IL1}	Interleukin-1 concentration, [pg/ml]	500
C_{IL2}	Interleukin-2 concentration, [pg/ml]	2
C_{IFN}	Interferon concentration, [IU/ml]	10^{-15}
C_K	Cortisol concentration, [nanogram/ml]	3.055
C_M	Macrophage (monocyte) concentration, [cells/ml]	10^{-15}
C_{NK}	NK-cell (natural killers) concentration, [cells/ml]]	10^{-15}
C_R	Number of resistant cells in a target organ, [cells]	$1.7 \cdot 10^{-11}$
C_{TH}	T-helper concentration, [cells/ml]	10^{-6}
C_V	Virus concentration, [copies/ml]	$1.7 \cdot 10^{-11}$

Interactions between cell populations and information molecules in the body are based on the clonal selection theory (Burnet theory); according to it, cell clones (B-cells), which are specific in respect of different viruses, appear in a body. A virus selectively contacts a relevant clone thus stimulating it to produce antibodies. They are also based on the mass action law (the reaction rate is proportionate to the product of substance concentrations) and on application of interaction properties and Markov's birth-death processes. All the variables were deprived of their dimensions via recalculating as per their constant homeostatic value (Table 1). As a result, all the variables in our mathematical model have the same order.

Healthy cells

The equation that defines how fast the number of healthy cells changes under virus invasion and an immune response can be written as follows:

$$\frac{dC_{HE}}{dt} = k_1(C_{HE} + C_R)C_D + k_2 C_R - k_3 C_{HE} C_{IFN} - k_4 C_{HE} C_V , \quad (1)$$

where C_{HE} is the number of healthy non-resistant cells in a target organ; C_R is the number of resistant cells in a target organ; C_D is the number of dead cells in a target organ; C_{IFN} is the interferon concentration; C_V is the virus concentration.

The summand $k_1(C_{HE} + C_R)C_D$ describes production of new healthy cells in a target organ. New healthy cells are generated due to reproduction of healthy and resistant cells. The number of dead cells can indirectly stimulate reproduction of uninfected cells due to macrophages releasing specific proteins in the process of dead cells absorption. These proteins stimulate cells reproduction in a target organ. The recovery (regeneration) coefficient for epithelial cells in respiratory tract is $k_1 = 4$ [1/day]; its value is based on the assumption that one cell division of an epithelial cells lasts for 0.3–1 day [34].

The summand $k_2 C_R$ describes an increase in the number of healthy cells due to transition of resistant cells into their normal healthy state. With time, resistant cells lose their resistance to a virus and return to their initial (healthy) state [35]. The coefficient describing the rate at which resistant cells turn into healthy ones in a target organ is $k_2 = 1$ [1/day] [31]. It is noteworthy that the coefficient k_2 is different for different tissues.

The summand $k_3 C_{HE} C_{IFN}$ determines the process through which a healthy cell becomes resistant. Transition of a healthy cell in a target organ into being resistant one occurs under interaction with interferon. The coefficient of healthy cells transition into being resistant is $k_3 = 0.01$ [1/day] [33].

The summand $k_4 C_{HE} C_V$ describes healthy cells loss as a result of their transition into being infected. Infection occurs when a virus and a healthy cell meet in a target organ. The coefficient of healthy cells infection is $k_4 = 0.34$ [1/day].

The model doesn't consider natural cells death; we assume that we can neglect this process at a time scale of infection. Average life span for epithelial cells in the respiratory tract amounts to 14 days. Certain models that describe long-term infection processes (for example, when T-helpers become target cells), [36, 37] incorporate summands like the following one: $-kC_{HE}$.

Infected cells

We apply the following equation to describe changes in the number of infected cells under an immune response:

Mathematical Biology and Bioinformatics. 2023. V. 18. № S. doi: 10.17537/2023.18.t17

$$\frac{dC_I}{dt} = k_4 C_{HE} C_V - k_5 C_{NK} C_I C_{IL2} \left(1 - k_8 \frac{C_K(t-T)}{1+C_K(t-T)}\right) - \\ - k_6 C_{CTL} C_I \left(1 - k_9 \frac{C_K(t-T)}{1+C_K(t-T)}\right) H(C_{CTL} - k_{46}) - k_7 C_I \quad , \tag{2}$$

where C_{NK} is the NK-cell (natural killers) concentration; C_I is the number of infected cells in a target organ; C_{IL2} is the intreleukin-2 concentration; C_K is the cortisol concentration; C_{CTL} is the concentration of cytotoxic T-lymphocytes.

Infection is described with a random meeting of a virus and a healthy cell in a target organ. It is given by the following equation member: $k_4 C_{HE} C_V$.

The summand $k_5 C_{NK} C_I C_{IL2} \left(1 - k_8 \frac{C_K(t-T)}{1+C_K(t-T)}\right)$ describes destruction of infected cells in a target organ with the help of NK-cells without occurrence of new viruses. Destruction takes place when an infected cell and a NK-cell meet. Interleukin-2 stimulates activity of NK-cells. Cortisol inhibits activity of NK-cells but its impacts occur with a time lag as its delivery from the adrenals to a target organ takes time. The time lag in occurrence of inhibiting effects produced by cortisol on NK-cells activity amounts to 19 minutes (T = 0.0132 [day]) [38]. The same time lag is used everywhere in this study based on the assumption that it takes cortisol the same amount of time to go all the way from the adrenals to a place where an infection develops. The coefficient k_5 = 0.05 [1/day] shows destruction of infected cells by NK-cells that are stimulated by interleukin-2. Inhibition of NK-cells by cortisol is determined with the coefficient k_8 = 0.5.

The following summand is applied to describe infected cells destruction with the help of cytotoxic T-lymphocytes: $k_6 C_{CTL} C_I \left(1 - k_9 \frac{C_K(t-T)}{1+C_K K(t-T)}\right) H(C_{CTL} - k_{46})$. Destruction takes place after an infected cell meets a cytotoxic T-lymphocyte and new viruses don't occur when a cell is destroyed. Cortisol inhibits cytotoxic T-lymphocytes. To describe an accumulation effect of these cells in lymph nodes until their amount reaches a certain level, we apply the Heaviside function, which is given as follows: $H(C_{CTL} - k_{46})$, where k_{46} = 1. The coefficient k_6 = 0.066 [1/day] describes how fast infected cells are destroyed by cytotoxic T-lymphocytes. The coefficient value is based on the fact that one cytotoxic T-lymphocyte can destroy on average 10 infected cells over its life span [33]. Inhibition of cytotoxic T-lymphocytes by cortisol is determined with the following coefficient: k_9 = 0.5.

It is noteworthy that cytotoxic T-lymphocytes are much more effective than NK-cells. The basic function of NK-cells is to restrain reproduction of viruses at the first stages of infection; this restrain gives time for the accumulation of the necessary cytotoxic T-lymphocytes amount.

The summand $k_7 C_I$ describes natural death of infected cells followed by release of new viruses. The coefficient k_7 = 1.5 [1/day]; it determines how fast an infected cell turns into a dead one. The coefficient value is based on the fact that an infected cell life span is equal to approximately one day [39].

Resistant cells

The equation that describes changes in the number of resistant cells can be written as follows:

$$\frac{dC_R}{dt} = k_3 C_{HE} C_{IFN} - k_2 C_R \, . \tag{3}$$

Transition of healthy cells into resistant ones due to impacts exerted on them by interferon is given with the following equation member: $k_3 C_{HE} C_{IFN}$.

The summand $k_2 C_R$ reflects how cells lose their resistance to infection after a limited period of time and return into their initial state in which they are sensitive to infection.

Interferon

We apply the following equation to describe changes in interferon concentrations under virus invasion:

$$\frac{dC_{IFN}}{dt} = k_{10} C_I - k_{11} C_{HE} C_{IFN} - k_{12} C_{IFN}. \quad (4)$$

Infected cells stimulate inborn immunity as they release α and β interferon molecules [32, 40, 41], which interact with healthy cells and give them resistance to an infection thus effectively preventing a virus from spreading. This mechanism gives the body necessary time to work out an adaptive immune response and to eliminate a virus completely.

Interferon production by infected cells is given by the summand $k_{10} C_I$. The coefficient $k_{10} = 2000$ [1/day] describes the process of interferon production by infected cells.

The summand $k_{11} C_{HE} C_{IFN}$ describes how interferon interacts with healthy cells in a target organ in order to make them resistant. Interferon impact on healthy cells is determined by the coefficient $k_{11} = 17$ [1/day] [33].

Natural decay of interferon is given by the last equation member $k_{12} C_{IFN}$. The coefficient of interferon natural decay is $k_{12} = 8$ [1/day] [33].

Dead cells

The following equation describes changes in the number of dead cells in a target organ under virus invasion:

$$\begin{aligned} \frac{dC_D}{dt} &= k_7 C_I + k_5 C_{NK} C_I C_{IL2} \left(1 - k_8 \frac{C_K(t-T)}{1 + C_K(t-T_2)}\right) + \\ &+ k_6 C_{CTL} C_I \left(1 - k_9 \frac{C_K(t-T)}{1 + C_K(t-T)}\right) H(C_{CTL} - k_{46}) - k_{13} C_D C_M \end{aligned}, \quad (5)$$

where C_M is the macrophage (monocyte) concentration.

The variable C_D gives a numeric description of tissue damages and is a parameter to describe severity of a disease [42, 43].

The summand $k_7 C_I$ characterizes natural death of infected cells after which new viruses are released. The coefficient $k_7 = 1.5$ [1/day]; it determines how fast infected cells die.

The summand $k_5 C_{NK} C_I C_{IL2} \left(1 - k_8 \frac{C_K(t-T)}{1 + C_K(t-T)}\right)$ describes destruction of infected cells in a target organ by NK-cells without occurrence of new viruses. The time lag of inhibiting effects produced by cortisol on NK-cells activity amounts to 19 minutes ($T = 0.0132$ [day]) [38]. The coefficient $k_5 = 0.05$ [1/day]; it describes destruction of infected cells by NK-cells stimulated by interleukin-2. Inhibition of NK-cell by cortisol is determined by the following coefficient: $k_8 = 0.5$.

To describe how infected cells are destroyed with the help of cytotoxic T-lymphocytes, the following summand is applied: $k_6 C_{CTL} C_I \left(1 - k_9 \frac{C_K(t-T)}{1 + C_K(t-T)}\right) H(C_{CTL} - k_{46})$. To describe

effects produced by retention of these cells in lymph nodes until their amount reaches a certain level, the following Heaviside function is applied: $H(C_{CIL} - k_{46})$, где $k_{46} = 1$.

The coefficient $k_6 = 0.066$ describes destruction of infected cells by cytotoxic T-lymphocytes. Inhibition of cytotoxic T-lymphocytes by cortisol is determined by the coefficient $k_9 = 0.5$. The coefficient value is determined based on conformity of the solution to the equation system with actual data on changes in parameters under a virus infection.

The summand $k_{13}C_DC_M$ describes how macrophages eliminate dead cells. The coefficient $k_{13} = 10$ [1/day] characterizes this elimination.

Antigen

The following equation describes changes in virus concentrations when an immune response occurs:

$$\frac{dC_V}{dt} = k_{14}C_I - k_{15}C_VC_A - k_{16}C_VC_{HE} - k_{17}C_V, \quad (6)$$

where C_A is the antigen concentration.

Production of viruses by infected cells is given with the summand $k_{14}C_I$. The coefficient of virus release by infected cells in a target organ is $k_{14} = 510$ [1/day]. The coefficient value is based on the fact that one infected cell releases approximately10^3–10^4 viruses a day [39].

The summand $k_{15}C_VC_A$ describes how viruses are neutralized by specific antibodies. The rate of interaction between viruses and antibodies is given with the coefficient $k_{15} = 6.192$ [1/day]. Its value is based on the fact that it takes 1–10 antibodies to neutralize one virus [44].

A decrease in the number of viruses due to them penetrating healthy cells is given by the following equation member: $k_{16}C_VC_{HE}$. The coefficient k_{16}, which characterizes a number of viruses necessary to infect a healthy cell, is equal to 1.02 [1/day]. According to *in vitro* experiments, it takes 1–10 viruses to infect one healthy cell [33]. The difference between the values of the coefficients k_4 and k_{16} occurs due to the fact that several viruses are required to infect a healthy cell.

The summand $k_{17}C_V$ describes non-specific removal of viruses, for example, with the help of coughing and other mechanisms. The coefficient that characterizes non-specific removal of viruses is as follows: $k_{17} = 3.4$ [1/day]. The coefficient value is determined by the fact that non-specific physical removal of a virus takes 4–24 hours [33].

Macrophages

We suggest the following equation to describe changes in the number of macrophages in a target organ:

$$\frac{dC_M}{dt} = k_{18}F_b - k_{19}C_M, \quad (7)$$

where F_b is functional capability of the bone marrow, its synthesizing function.

As it is rather difficult to determine macrophage quantities in various organs and systems using laboratory tests, we chose monocyte count in blood as an examined variable in the model. Monocyte count is directly proportionate to macrophage quantities in various organs as all the ‘non-specialized’ monocytes turn into ‘specialized’ macrophages.

The first equation member $k_{18}F_b$ describes macrophage production allowing for lower intensity of the blood-making function performed by the bone marrow when there are functional disorders in it. The macrophage production coefficient is assumed to be equal to $k_{18} = 0.03$ [1/day]. Functionality of the bone marrow as regards monocyte production is described with the parameter F_b.

The last equation member $k_{19}C_M$ characterizes the death mechanism related to the end of a macrophage life span. The coefficient $k_{19} = 0.03$ [1/day] describes natural excretion of macrophages [31]. The macrophage lifecycle varies between 14 and 60 days; when it's complete, they are destroyed and excreted by the liver.

Interleukin-1

We suggest the following equation to describe the interleukin-1 concentration:

$$\frac{dC_{IL1}}{dt} = k_{20}C_M C_D\left(1 - k_{21}\frac{C_K(t-T)}{1+C_K(t-T)}\right) - k_{22}C_{IL1}, \quad (8)$$

where C_{IL1} is the interleukin-1 concentration.

To describe the mechanism of interleukin-1 production, we apply the following summand: $k_{20}C_M C_D\left(1 - k_{21}\frac{C_K(t-T)}{1+C_K(t-T)}\right)$. When interacting with dead cells, macrophages release interleukin-1 into blood, and cortisol exerts inhibiting impacts on this process. The more dead cells occur in the body, the more frequently they interact with macrophages, and the more interleukin-1 is released. The coefficient $k_{20} = 0.145$ [1/day] characterizes interleukin-1 production by macrophages [45]. The time lag in inhibiting effects by cortisol on interleukin-1 production amounts to 19 minutes ($T = 0.0132$ [day]). Inhibition of macrophage functions by cortisol is determined by the coefficient $k_{21} = 0.5$.

The summand $k_{22}C_{IL1}$ describes interleukin-1 decay in the liver; the products of this decay can be partially excreted by the kidneys. The coefficient that describes natural decay of interleukin-1 is taken as $k_{22} = 0.1245$ [1/day] [46].

T-helpers

The equation that describes changes in the concentration of T-helpers can be given as follows:

$$\frac{dC_{TH}}{dt} = k_{23}F_b - k_{24}C_{TH}, \quad (9)$$

where C_{TH} is the T-helper concentration.

Interleukin-2 production is assumed to be the key function performed by T-helpers in the suggested model.

The first equation member $k_{23}F_b$ describes T-helper production by the bone marrow. Functionality of the bone marrow concerning monocyte production is described with the parameter F_b. The coefficient $k_{23} = 0.0058$ [1/day] determines intensity of T-helper production by the bone marrow.

The last equation member $k_{24}C_{TH}$ characterizes natural death of T-helpers. The macrophage lifecycle is approximately 170 days; when it is completed, they are destroyed and excreted by the liver. The coefficient $k_{24} = 0.0058$ [1/day] describes natural excretion of T-helpers.

Interleukin-2

Active reproduction of immune response cells takes place after the body gives the first signals that a virus infection has occurred; it happens due to stimulating influence exerted by interleukin-2. We suggest the following equation to describe changes in the interleukin-2 concentration:

$$\frac{dC_{IL2}}{dt} = k_{25}C_{TH}C_{IL1} - k_{26}C_{IL2}. \quad (11)$$

We use the summand $k_{25}C_{TH}C_{IL1}$ to describe how interleukin-2 is produced by T-helpers. Interleukin-2 is produced when T-helpers are stimulated by interleukin-1. The coefficient $k_{25} = 0.328$ [1/day] describes how T-helpers produce interleukin-2.

The summand $k_{26}C_{IL2}$ describes natural decay of interleukin-2 in the liver. The coefficient $k_{26} = 0.248$ [1/day] determines how fast interleukin-2 decays.

NK-cells

We suggest the following equation to describe changes in the NK-cell concentration:

$$\frac{dC_{NK}}{dt} = k_{27}F_b - k_{28}C_{NK}\,. \tag{12}$$

NK-cells take part in non-specific protection of the body against viral intracellular pathogens. They eliminate all cells that fail to be recognized with the 'friend or foe' system. The suggested equation describes NK-cell production by the bone marrow and their natural death.

The summand $k_{27}F_b$ describes NK-cell production considering its lower intensity in case the blood-making function of the bone marrow has deteriorated. The coefficient $k_{27} = 0.11$ [1/day] describes NK-cell production by the bone marrow.

Natural death of NK-cells is described with the summand $k_{28}C_{NK}$. The NK-cell lifecycle is approximately 7–10 days; when it is completed, they are destroyed and excreted by the liver. The coefficient $k_{28} = 0.11$ [1/day] describes natural death of NK-cells.

Cytotoxic T-lymphocytes

When the body is healthy, effector cells are in lymph nodes and blood. But when an infection occurs, they are activated and migrate into infected tissues. The following equation describes changes in the concentration of cytotoxic T-lymphocytes under an immune response:

$$\begin{aligned}\frac{dC_{CTL}}{dt} &= k_{29} + k_{30}C_{CTL}C_{IL2} - k_{32}C_{CTL} - \\ &- k_{31}C_{CTL}C_I\left(1 - k_9\frac{C_K(t-T)}{1+C_K(t-T)}\right)H\left(C_{CTL} - k_{46}\right)\end{aligned}\,. \tag{13}$$

The summand $k_{29} = 0.4$ [1/day] characterizes natural (background) production of cytotoxic T-lymphocytes necessary to maintain minimum level of such cells when there is no infection in the body [31].

The summand $k_{30}C_{CTL}C_{IL2}$ describes reproduction of cytotoxic T-lymphocytes stimulated by interleukin-2 when there is an infection in the body. The coefficient of cytotoxic T-lymphocyte reproduction under interleukin-2 effects is as follows: $k_{30} = 8.3$ [1/day] [31].

To describe a decrease in the number of cytotoxic T-lymphocytes while they destroy infected cells, we apply the following summand: $k_{31}C_{CTL}C_I\left(1 - k_9\frac{C_K(t-T)}{1+C_K(t-T)}\right)H\left(C_{CTL} - k_{46}\right)$.

To describe the effect of these cells accumulating in lymph nodes until their quantity reaches a certain level, the following Heaviside function is applied: $H\left(C_{CTL} - k_{46}\right)$, where $k_{46} = 1$. The coefficient $k_{31} = 109.3$ [1/day] describes how cytotoxic T-lymphocytes are destroyed when they interact with infected cells. The coefficient value is based on the fact that one cytotoxic T-lymphocyte can destroy approximately 100 infected cells [33]. Inhibition of cytotoxic T-cells by cortisol is determined by the coefficient $k_9 = 0.5$.

Natural death of cytotoxic T-lymphocytes is described by the summand $k_{32}C_{CTL}$. The cytotoxic T-lymphocyte lifecycle is approximately 2–3 days; after it is completed, they are destroyed and excreted by the liver. The coefficient $k_{32} = 0.4$ [1/day] describes natural death of cytotoxic T-lymphocytes [33].

B-cells

We suggest the following equation to describe changes in the B-cell concentration:

$$\frac{dC_B}{dt} = k_{47} + k_{33}C_B C_{IL2} - k_{34}C_B, \tag{14}$$

where C_B is the B-cell concentration.

Macrophages stimulate adaptive immunity by activating reproduction of virus-specific B-cells able to produce antibodies [47].

The summand $k_{47} = 0.4$ [1/day] characterizes natural (background) reproduction of B-cells necessary to maintain minimum level of such cells when there is no infection in the body [31].

B-cell reproduction stimulated by interleukin-2 in case an infection occurs in the body is described by the following summand: $k_{33}C_B C_{IL2}$. The coefficient of B-cell reproduction under interleukin-2 effects is given as follows: $k_{33} = 11.5$ [1/day] [31].

The summand $k_{34}C_B$ describes natural death of B-cells. The B-cell lifecycle is approximately 2-3 days; after it is completed, they are destroyed and excreted by the liver. The coefficient $k_{34} = 0.4$ [1/day] describes natural death of B-cells [31].

Antibodies

The equation that characterizes changes in the relative concentration of antibodies can be written as follows:

$$\frac{dC_A}{dt} = k_{35}C_B\left(1 - k_{36}\frac{C_K(t-T)}{1+C_K(t-T)}\right)H(C_B - k_{45}) - k_{37}C_V C_A - k_{38}C_A. \tag{15}$$

Antibodies play the leading role in fighting against a virus neutralizing it before it infects cells in a target organ whereas NK-cells and cytotoxic T-lymphocytes are responsible for removing infected cells thereby preventing a virus from reproducing itself [48].

The summand $k_{35}C_B\left(1 - k_{36}\frac{C_K(t-T)}{1+C_K(t-T)}\right)H(C_B - k_{45})$ characterizes production of antibodies by B-cells. Cortisol inhibits production of antibodies and this effect occurs after a time lag resulting from spatial location of organs. The time lag in inhibiting effects by cortisol on interleukin-1 production amounts to 19 minutes ($T = 0.0132$ [day]).

To describe the effect of production of antibodies by B-cells that starts only after the B-cell amount reaches a certain level, we apply the following Heaviside function: $H(C_B - k_{45})$, where $k_{45} = 1$. The coefficient $k_{35} = 0.043$ [1/day] describes production of antibodies by B-cells allowing for inhibiting effects of cortisol [31]. Intensity of B-cell inhibition by cortisol is determined with the coefficient $k_{36} = 0.5$.

The summand $k_{37}C_V C_A$ describes how viruses are neutralized by specific antibodies. Virus neutralization by antibodies is determined by the following coefficient $k_{37} = 146.2$ [1/day] [33].

The summand $k_{38}C_A$ is applied to describe natural decay of antibodies. Decay of antibodies occurs in the liver; decay products can be partially excreted by the kidneys. The coefficient that describes natural decay of antibodies is $k_{38} = 0.043$ [1/day] [31].

Corticoliberin

We apply the following equation to describe changes in the corticoliberin concentration under a virus infection:

$$\frac{dC_{CRH}}{dt} = F_h\left(1 - k_{39}\frac{C_K(t-T)}{1+C_K(t-T)}\right)(1+k_{40}C_{IL1}) - k_{41}C_{CRH}\,, \qquad (16)$$

where F_h is the functional capacity of the hypothalamus, its synthesizing function;
C_{CRH} is the corticoliberin concentration.

Increased interleukin-1 levels in blood lead to a higher rate of corticoliberin production by the hypothalamus. And here four processes exert their influence on the rate of changes in the corticoliberin concentration in a body: natural (background) corticoliberin production, synthesis due to the hypothalamus being stimulated with interleukin-1, a weaker synthesizing function of the hypothalamus, and inhibition of synthesis by a high cortisol concentration and natural excretion of corticoliberin out of the body.

The first summand in the equation $F_h\left(1 - k_{39}\frac{C_K(t-T)}{1+C_K(t-T)}\right)(1+k_{40}C_{IL1})$ describes corticoliberin production by the hypothalamus allowing for the effects exerted by cortisol, interleukin-1, and the synthesizing function of the hypothalamus F_h. Cortisol inhibits the hypothalamus activity; its effects occur with a time lag as its delivery from the adrenals to a target organ takes time. This time lag in inhibiting effects by cortisol on the hypothalamus activity is equal to 19 minutes ($T = 0.0132$ [day]). The coefficient $k_{39} = 0.5$ describes intensity of the hypothalamus inhibition by cortisol and corticoliberin production inhibition. Stimulating effects exerted by interleukin-1 on corticoliberin production are determined with the coefficient $k_{40} = 1$.

The second summand $k_{41}C_{CRH}$ is responsible for natural corticoliberin excretion out of the body. The natural corticoliberin excretion coefficient is assumed to be equal to $k_{41} = 3.7669$ [1/day]. The coefficient value is determined based on the fact that a period of partial corticoliberin excretion in the human body is equal to 4 minutes [49].

Adrenocorticotropic hormone

We apply the following equation to describe changes in the adrenocorticotropic hormone concentration:

$$\frac{dC_{ACTH}}{dt} = F_p\left(1 - k_{42}\frac{C_K(t-T)}{1+C_K(t-T)}\right)C_{CRH} - k_{43}C_{ACTH}\,, \qquad (17)$$

where F_p is the functional capacity of the hypothesis, its synthesizing function;
C_{ACTH} is the adrenocorticotropic hormone (ACTH) concentration.

Corticoliberin activates production of the adrenocorticotropic hormone by the hypophysis; in its turn, cortisol inhibits the secretory function of the hypophysis.

The summand $F_p\left(1 - k_{42}\frac{C_K(t-T)}{1+C_K(t-T)}\right)C_{CRH}$ describes production of the adrenocorticotropic hormone by the hypophysis under effects exerted on it by corticoliberin. Cortisol inhibits production of the adrenocorticotropic hormone; its effects occur with a time lag caused by the spatial location of the hypophysis and the adrenals that produce cortisol. Impaired synthesizing function of the hypothesis F_p results in lower production of the adrenocorticotropic hormone. The time lag in inhibiting effects of cortisol on the hypophysis activity amounts to 19 minutes ($T = 0.0132$ [day]). The coefficient $k_{42} = 0.5$ describes

intensity of the hypothesis inhibition by cortisol and inhibition of the adrenocorticotropic hormone production.

The summand $k_{43}C_{ACTH}$ describes natural decay of the adrenocorticotropic hormone. The coefficient for natural excretion of the adrenocorticotropic hormone is as follows: $k_{43} = 0.75716$ [1/day]. The coefficient value is determined based on the fact that a period of partial excretion of the adrenocorticotropic hormone from the human body is approximately 20 minutes [50].

Cortisol

The following equation describes changes in the cortisol concentration:

$$\frac{dC_K}{dt} = F_a C_{ACTH}(t-T) - k_{44}C_K, \tag{18}$$

where F_a is the functional capacity of the adrenals, their synthesizing function.

The adrenocorticotropic hormone influences the adrenals and they start producing cortisol under this stimulation.

The summand $F_a C_{ACTH}(t-T)$ describes how the rate of cortisol production increases when the adrenocorticotropic hormone level grows allowing for a time lag caused by spatial location of the adrenals. Impaired synthesizing function of the adrenals F_a influences the rate of cortisol production. The time lag in inhibiting effects exerted by the adrenocorticotropic hormone on the adrenals activity is equal to 19 minutes ($T = 0.0132$ [day]).

Natural decay of cortisol is described by the summand $k_{44}C_K$. The coefficient of natural excretion of cortisol from the body is $k_{44} = 0.19722$ [1/day]. The coefficient value is based on the fact that a period of partial cortisol excretion from the human body is equal to approximately 76 minutes [50].

The equations system with the following initial conditions: $(C_{HE}(0) = C_{HE,0}$, $C_I(-T,0) = C_{I,0}$, $C_R(0) = C_{R,0}$, $C_V(0) = C_{V,0}$, $C_{IFN}(0) = C_{IFN,0}$, $C_D(-T,0) = C_{D,0}$, $C_M(0) = C_{M,0}$, $C_{IL1}(-T,0) = C_{IL1,0}$, $C_{TH}(0) = C_{TH,0}$, $C_{IL2}(0) = C_{IL2,0}$, $C_{NK}(0) = C_{NK,0}$, $C_{CIL}(-T,0) = C_{CIL,0}$, $C_B(0) = C_{B,0}$, $C_A(-T,0) = C_{A,0}$, $C_{CRH}(-T,0) = C_{CRH,0}$, $C_{ACTH}(-T,0) = C_{ACTH,0}$, $C_K(-T,0) = C_{K,0})$ is a Cauchy problem written for a system of the first order ordinary differential equations with a retarded argument. To solve the outlined Cauchy problem, we apply implicit numerical technique by Runge-Kutta of the third order – RadoIIA. This algorithm belongs to a group of algorithms applied for solving stiff systems of differential equations with a retarded argument.

Description of effects produced by the initial level of viruses (initiating virus concentration)

We have examined what influence the initial virus concentration would have on the outbreak, duration, and severity of an infectious disease. The aim was to get an insight into dynamics of an immune response produced by the human body as an antiviral reaction. Having analyzed the results obtained in the previous studies, we established that virus infection of the body can lead to different states of being sick; however, reasons for different clinical courses of an infectious disease have not been fully studied yet [51].

Figures 2–3 show clearly that dynamics of an immune response falls into one of three conventional categories depending on the initial virus concentration $C_V(0)$: a symptomless disease, a typical disease (an average clinical course) and a severe disease [52]. If the initial virus concentration $C_V(0)$ is below the threshold value V_1, a disease does not develop. In this

case, an infection is symptomless and a virus does not reproduce in the body. An infected person is not considered infectious since a virus is rapidly removed from the body; its concentration remains very low and hardly causes any subsequent damage to a target organ. When the virus concentration $C_V(0)$ varies between $6.3 \cdot 10^{-5}$ and $5 \cdot 10^{-3}$, the relationships $C_D(t)$ follow similar trajectories but the higher $C_V(0)$ is, the faster a disease develops.

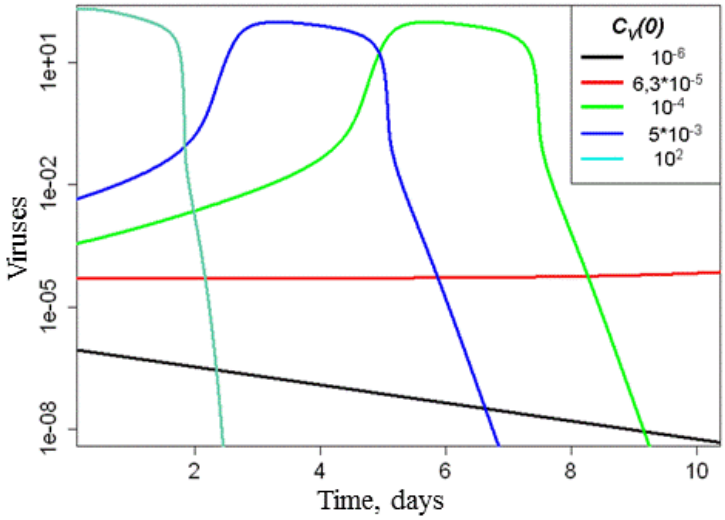

Fig. 2. The relationship between the standardized virus concentration in the body and time under different initial virus concentrations

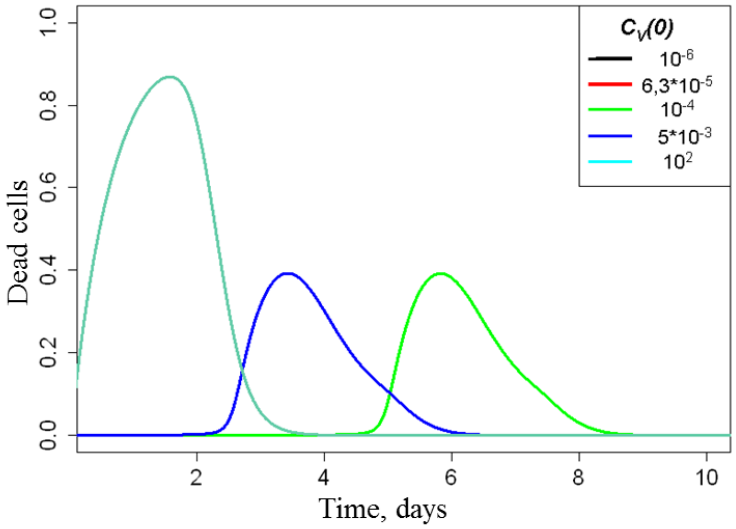

Fig. 3. The relationship between damage of a target organ and time under different initial virus concentrations

If the initial virus concentration $C_V(0)$ is between V_1 and V_2 (a value separating an average and severe clinical course of a disease), disease dynamics follows similar trajectories; but the higher $C_V(0)$ is, the faster a disease develops (apparent symptoms). In other words, within this range of $C_V(0)$, the maximum virus concentration is $C_{V,\max} = 86$, the maximum damage of a target organ is $C_{D,\max} = 0.4$, duration of a disease (apparent symptoms) as a period of time when a person is an infection source does not depend on the initial virus

concentration. Damage of a target organ does not show under these scales when the initial virus concentration is equal to 10^{-6} and $6.3\cdot10^{-5}$.

If the initial virus concentration $C_V(0)$ is higher than V_2, dynamics of an infection corresponds to a severe clinical course. In this case, the maximum virus concentration and damage of a target organ depend on the initial virus concentration (any growth in the initial virus concentration results in the higher maximum damage of a target organ). The maximum damage can exceed 40% of cells in a target organ. Such damage levels are hazardous since they create favorable conditions for secondary infections, which, in their turn, can cause death.

In this study, the threshold values $V_1 = 6.3\cdot10^{-5}$, $V_2 = 10^{-4}$ and $V_3 = 5\cdot10^{-3}$ are applied for the analyzed parameters; the initial virus concentration V_1 creates a trajectory that ends at the saddle knot point, and V_1 itself is an approximate value determined as the lowest $C_V(0)$ value for which a trajectory deviates substantially from its typical behavior.

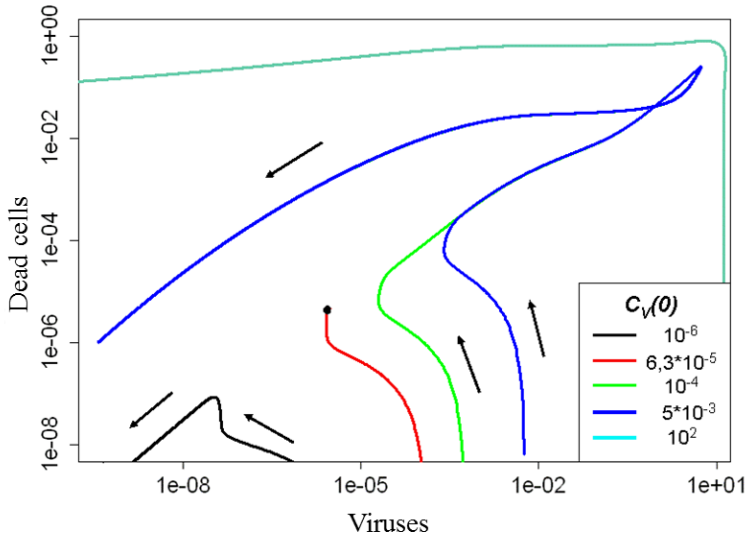

Fig. 4. The phase diagram showing the standardized virus concentration and damage of a target organ under different initial virus concentration or viral load $C_V(0)$. Time direction is shown by the arrow.

Figure 4 presents the project of the phase diagram on the variables C_V and C_D. In this projection, the trajectories have only limited tendency to cross. The trajectories for the initial conditions $V_1 < C_V(0) < V_2$ coincide in accordance with observation that the trajectories are very similar and are only shifted in time. In this graph, the trajectory with $C_V(0) = V_1$ ends at the point (C_V, C_D) = ($2.7\cdot10^{-6}$, $9\cdot10^{-6}$). The maximum virus concentration and the maximum damage of a target organ equal $C_{V,\max} = 86$ and $C_{D,\max} = 0.4$ under an average clinical course.

SENSITIVITY ANALYSIS

Analysis of solution sensitivity to parameters that describe a virus

Dynamics of a virus concentration is influenced by the summands $k_4 C_{HE} C_V$ and $k_{14} C_I$ that describe how fast a target organ is being infected and how fast infected cells produce new viruses. When virulence (a virus ability to infect) is high, viruses are able to infect healthy cells much faster and they also reproduce themselves in infected cells at a higher rate. Since sensitivity to changes in k_4 and k_{14} is qualitatively the same in its essence due to both these parameters determining rates of changes in virus concentrations in the body, we suggest

considering only the parameter k_4 Any change in the parameter k_4 influences ranges of initial virus concentrations $C_V(0)$ that induce a disease of average severity.

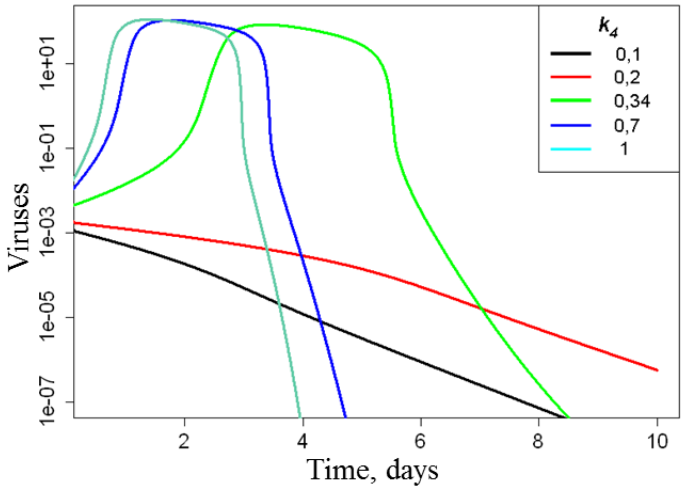

Fig. 5. The relationship between the standardized virus concentrations in the human body and time under different values of the coefficient k_4 . The initial virus concentration is $5 \cdot 10^{-3}$.

When the k_4 value is three times higher than the basic value (highly virulent strains), then, regardless of an initial virus concentration, a disease develops in any case (Fig. 5). When the parameter k_4 is three times lower than the basic value, all three types of a clinical course can occur depending on the value $C_V(0)$: symptomless, average, and severe. When the value $C_V(0)$ is low, a disease does not have any symptoms. The higher virulence is, the earlier a disease develops and the shorter its duration is. Figure 6 shows a relationship between damage of a target organ and time under different values of the coefficient. The difference between the maximum damage of a target organ, $C_{D,\max}$, is significant for low and high values of the parameter k_4 (solutions to the equations with different values of the identified a more than two-time difference between $C_{D,\max} = 0.6$ for $k_4 = 1$ and $C_{D,\max} = 0.23$ for $k_4 = 0.34$). These results were quite expected; infection caused by a highly virulent virus leads to substantial damage whereas infection caused by a virus with low virulence can remain unnoticed. Damage of a target organ does not become obvious under such scales when the value of the parameter k_4 is below 0.34.

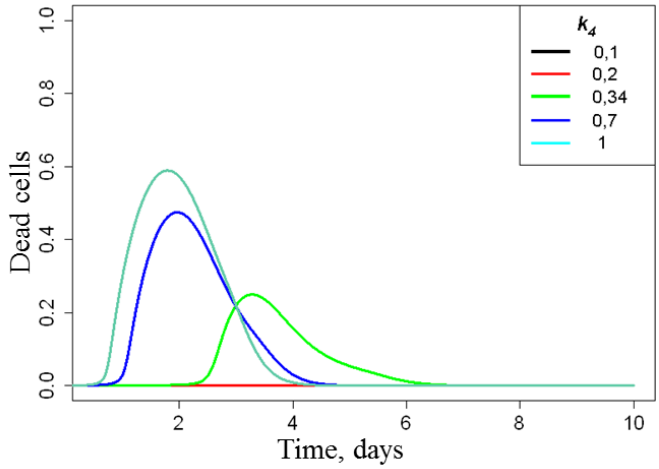

Fig. 6. The relationship between damage of a target organ and time under different values of the coefficient k_4 . The initial virus concentration is $5 \cdot 10^{-3}$.

The lower virulence is, the longer a period is between infection and recovery. Duration of a disease (after symptoms have become apparent) and the maximum virus concentration in the body are not sensitive to changes in virulence.

Figure 7 provides the phase diagram for solutions to the system of differential equations (1)–(18) at $k_4 = 1$. It is the same in its essence as that shown in Figure 4. The threshold point in dynamics between an average disease and a symptomless one is associated with the unstable threshold state x_2. Dynamics of changes in the parameters is shown with the arrows. The maximum virus concentration and the maximum damage of a target organ equals $C_{V,\max} = 110$ and $C_{D,\max} = 0.6$ accordingly in case of an average clinical course.

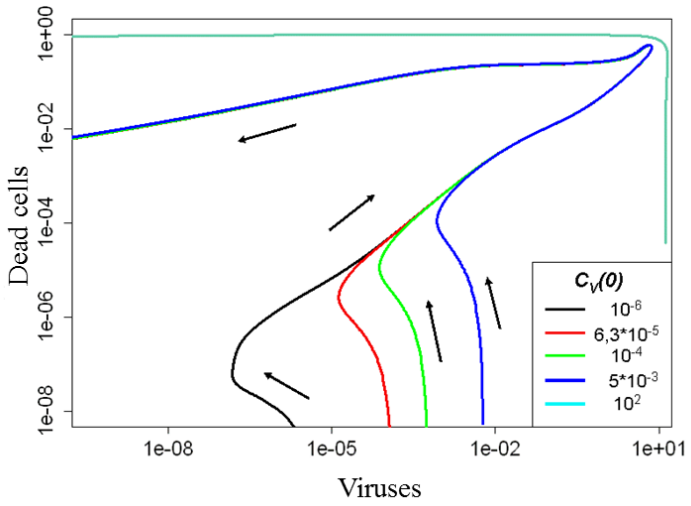

Fig. 7. The phase diagram of the standardized virus concentration and damage of a target organ under different initial virus concentrations (viral load) $C_V(0)$ when $k_4 = 1$. Dynamics of changes in the parameters is shown with the arrows.

Analysis of solution sensitivity to the parameters that describe interferon reactions

The summands $k_{10}C_I$ and $k_{11}C_{HE}C_{IFN}$ describe how fast interferon is produced and resistance is induced in cells of a target organ (the equation (4)). If k_{10} deviates from its standard value getting above or below it, a disease always develops under the standard values of $C_V(0)$. However, if the k_{11} value is above standard, a disease remains symptomless. A moment when a disease starts does not depend on values of the coefficients k_{10} and k_{11}, but when one of them becomes higher, duration of a disease shortens. The maximum damage of a target organ grows in case values of the coefficients k_{10} and k_{11} decline. Very low values of k_{10} and k_{11} lead to excessive damage of a target organ (more than 50 %), and this is likely to result in secondary infections or even death. Dynamics of the virus concentration is sensitive to the values of k_{10} and k_{11}: higher values of the parameters are associated with lower spread of viruses but longer duration of a disease.

When the rate constant of interferon production is two times higher than its basic value (that is, $k_{10} = 3000$), then a patient remains sick for approximately 3.5 days. When this rate is two times lower than its basic value (that is, $k_{10} = 1000$), a disease lasts for approximately 2.3 days (a disease is over sooner, but considerable damage is done to the body). Therefore, difference in duration of an infectious period is significant for different levels of inborn immunity. Even when an inborn immune response is absent (when $k_{10} = 0$ and $k_{11} = 0$), ultimately a disease is treated by an adaptive immune response and the body moves towards health.

Analysis of solution sensitivity to the parameters that describe the cellular component of inborn immunity

The summands $k_{27}F_b$ и $k_5C_{NK}C_IC_{IL2}$ describe how fast NK-cells are produced and how fast infected cells are removed by them. When a value of k_{27} or k_5 is quite high, the body can overcome a disease without any symptoms or typical signs provided that the initial virus concentration $C_V(0)$ is standard. Although the value of the parameter k_5 does not influence the beginning of a disease (occurrence of symptoms), when the constant of infected cell removal is high, a disease usually starts later. When the values of k_{27} and k_5 are low, a cellular response is less apparent, and symptoms of a disease persist longer. When the value of the parameter k_{27} is high, the maximum damage of the body $C_{D,\max}$ is also high and can cause death. On the other hand, when the value of k_5 is high, damage of cells in a target organ tends to be lower. Even if a decline in the parameter k_5 is significant, the value $C_{D,\max}$ remains below 0.4; consequently, a decline in the parameter does not influence mortality. Even if a cellular response is absent (when $k_{27} = 0$ and $k_5 = 0$), ultimately a virus is destroyed by inborn and adaptive immune responses, and the body moves towards health.

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 adequately. This model is a simplified variant of a complicated multi-component interaction between regulatory systems when virus invasion occurs under chemical contamination. However, it provides a qualitative picture of multi-component interaction between regulatory systems under developing inflammatory reactions of viral genesis. Basing on it, in future we plan to expand the model component structure possibly performing population analysis of a relationship between incidence of infection diseases and chemical contamination.

We have performed mathematical analysis of the general system of equations describing interactions between the neuroendocrine and immune systems. We have accomplished qualitative examination of the mathematical model that included analysis of the problem dimensions, identification of some specific points, and sensitivity analysis. All the variables were made dimensionless via recalculating as per their constant homeostatic value. We analyzed influence exerted by changes in the parameters on qualitative behavior of the solution results obtained by using the suggested mathematical model.

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