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System analysis and mathematical modeling of the disease caused by the 2019-nCoV coronavirus strain

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Abstract

A particular problem at the beginning of the second millennium is the epidemic caused by coronaviruses. In 2002-2003, new strains of viruses appeared – SARS-CoV SARS, in 2012, MERS-CoV. In 2019-2020, the epidemic caused by the coronavirus strain 2019-nCoV, which belong to the Beta-CoV group, is a threat. Different types of coronaviruses infect humans, cats, birds, dogs, cattle, pigs and hares, bats, camels and other animals. Coronaviruses have a single-stranded RNA genome, which encodes 4–5 structural proteins, including proteins of the outer membrane, matrix and small membrane. The complete 2019-nCoV genome is stored online at GenBank: MN908947.3. Coronaviruses have some unique features in RNA transcription. The RNA minus chain serves as a matrix for the synthesis of both new genomic and subgenomic RNAs. To develop a model of human resistance to the disease caused by the coronavirus family, elements, connections and ways of protecting the Human-Virus-Environment system were identified. The destructive functions of sixteen non-structural and structural proteins of the strain 2019-nCoV are considered. Deterministic and statistical models of the development of the danger of infection of the cells have been developed. A parameterized system for protecting a person from coronavirus damage has been developed.

1. Introduction

One of the most important problems of 2019-2020 is the search for optimal methods for creating protective functions of a person from coronavirus damage. The use of systems analysis methods is one of the promising ways to consider and solve the problems of combating viral infection in the face of uncertainty [1]. Currently, about 40 types of viruses are known, combined into 4 subfamilies. They bear this name because of the structure of their outer shell in the form of a crown. Coronaviruses - viruses with a positive RNA chain (+ RNA), in comparison with other RNA viruses, have an exceptionally large genome and have a unique replication mechanism. Viral particles of strain 2019-nCoV have a spherical shape with a diameter of 60-120 nm. The height of the protrusions is 9–12 nm.

2. Development of a model of the Human-Virus-Environment (HVE) system

Among viruses, coronaviruses are of particular danger. When developing a vaccine for the coronavirus family, it is necessary to have a methodology for studying the characteristics and assessing the state of human life. To formalize the elements of the HVE system, we introduce the following sets (Fig. 1):

$$\begin{aligned}
 H &= \{h_1, h_2, \dots, h_l\} && \text{– many types of people;} \\
 V &= \{v_1, v_2, \dots, v_n\} && \text{– coronavirus family;} \\
 E &= \{e_1, e_2, \dots, e_m\} && \text{– many environmental elements;} \\
 U &= \{u_1, u_2, \dots, u_l\} && \text{– many controls.}
 \end{aligned}$$

Figure 1. The relationship of the elements of the studied HVE system

The relationship between the elements of the system is defined by the binary relations R (1), by which we can understand the functional relations, preferences, successions, and others, reflecting the essence of the relationship between the elements of the HVE system:

$$\begin{aligned}
 &VR_H^{VH}, && VR_E^{VE} \\
 &UR_E && UR_H, \\
 &ER_H^{EH} &&
 \end{aligned} \tag{1}$$

Binary relations can be decomposed into more complex ones with the introduction of an additional variable C , called a state. We decompose the binary relations R into two subsets: a healthy (1) and an infected (2) cell. A cell, like any real system, functions in certain physiological conditions determined by the environment. In this case, system (1) is transformed as follows:

$$\begin{aligned}
 &VR_H^{V1}[C_H^V, H^1], C_H^V R_H^{V2} H^2 \\
 &VR_E^{V1}[C_E^V, E^1], C_E^V R_E^{V2} E^2 \\
 &ER_V^{E1}[C_V^E, H^1], C_V^E R_V^{E2} H^2
 \end{aligned} \tag{2}$$

The security of the HVE system and the state (C) of each element as a whole depend on their properties, which change during the life cycle of the HVE system.

$$\begin{aligned} C_H &= F_1[\{S_H\}, C_H^V, C_H^E], \\ C_E &= F_2[\{S_E\}, C_E^V]. \end{aligned} \quad (3)$$

The state of the HVE system is determined by the properties of the elements of the system (C_V, C_E, C_H). The nature of the change in these properties during the life cycle of the HVE system, as a rule, worsens due to cell aging and a decrease in protective abilities. Therefore, to build the dependences of real state changes in the HVE system, it is necessary to know some functional $\mathfrak{Z}$ that would determine the safe state of the HVE system and its properties:

$$C_{HVE} = \mathfrak{Z}(C_V, C_E, C_H). \quad (4)$$

The state of the C_V destructive elements of coronaviruses affects the state of the C_{HVE} system: α -, β -, γ -, δ -CoVs, which have certain chemical and biological properties; on the own state of C_H cells, depending on the protective functions of the cell, climatogeographic features of human habitation and relationships with animals - C_E .

3. Study of the model for assessing the state of the HVE system

The state of the HVE system is described by the functional characterizing the state of the arrays of elements (4). We are investigating human security in more detail. The state of human safety (C_H) depends on the safety index of one's own properties (Θ_H); changes in the safety index from the influence of coronaviruses ($\Delta\Theta_H(V)$); from a change in the safety indicator, depending on changes in environmental parameters ($\Delta\Theta_H(E)$) and is determined by the formula

$$C_H = \Theta_H + \Delta\Theta_H(V) + \Delta\Theta_H(E). \quad (5)$$

Let us describe in more detail the elements of equation (5).

The intrinsic properties of a cell (Θ_H) are determined by the susceptibility to destruction (modification) of nucleic acid elements that ensure the storage and transmission of genetic information (DNA and RNA) from exposure to coronavirus.

The change in the safety indicator $\Delta\Theta_H(V)$ depends on the group and strain of coronaviruses and is described by the equation

$$\Delta\Theta_H(V) = \frac{\partial\Theta_H}{\partial v_\alpha} \Delta v_\alpha + \frac{\partial\Theta_H}{\partial v_\beta} \Delta v_\beta + \frac{\partial\Theta_H}{\partial v_\gamma} \Delta v_\gamma + \frac{\partial\Theta_H}{\partial v_\delta} \Delta v_\delta, \quad (6)$$

where

$v_\alpha = \{\text{HCoV - 229E, HCoV - NL63, TGEV}\}$ – many coronaviruses α - of type;

$$v_{\beta} = \left\{ \begin{array}{l} \text{Bat - SL ZXC21, 2019-nCoV,} \\ \text{SARS-CoV, MERS-CoV} \end{array} \right\} \quad - \text{many coronaviruses } \beta\text{- of type;}$$

$$v_{\gamma} = \{\text{IBV, SW1}\} \quad - \text{many coronaviruses } \gamma\text{- of type;}$$

$$v_{\delta} = \{\text{HKU11, HKU17}\} \quad - \text{many coronaviruses } \delta\text{- of type.}$$

Of particular danger is the 2019-nCoV strain, which has a high destructive feature of the modification of nucleic acid elements, cell degradation, cleavage of polypeptides and other functions [2]. Consider the destructive functions of sixteen non-structural and structural proteins (nsp) of the coronavirus strain 2019-nCoV:

$$\begin{aligned} \Delta V_{2019\text{-nCoV}}(\text{nsp}) = & \frac{\partial v_{\beta}}{\partial(\text{nsp}_1)} \Delta \text{nsp}_1 + \frac{\partial v_{\beta}}{\partial(\text{nsp}_2)} \Delta \text{nsp}_2 + \frac{\partial v_{\beta}}{\partial(\text{nsp}_3)} \Delta \text{nsp}_3 + \frac{\partial v_{\beta}}{\partial(\text{nsp}_4)} \Delta \text{nsp}_4 + \\ & + \frac{\partial v_{\beta}}{\partial(\text{nsp}_5)} \Delta \text{nsp}_5 + \frac{\partial v_{\beta}}{\partial(\text{nsp}_6)} \Delta \text{nsp}_6 + \frac{\partial v_{\beta}}{\partial(\text{nsp}_7)} \Delta \text{nsp}_7 + \frac{\partial v_{\beta}}{\partial(\text{nsp}_8)} \Delta \text{nsp}_8 + \frac{\partial v_{\beta}}{\partial(\text{nsp}_9)} \Delta \text{nsp}_9 + \\ & + \frac{\partial v_{\beta}}{\partial(\text{nsp}_{10})} \Delta \text{nsp}_{10} + \frac{\partial v_{\beta}}{\partial(\text{nsp}_{11})} \Delta \text{nsp}_{11} + \frac{\partial v_{\beta}}{\partial(\text{nsp}_{12})} \Delta \text{nsp}_{12} + \frac{\partial v_{\beta}}{\partial(\text{nsp}_{13})} \Delta \text{nsp}_{13} + \\ & + \frac{\partial v_{\beta}}{\partial(\text{nsp}_{14})} \Delta \text{nsp}_{14} + \frac{\partial v_{\beta}}{\partial(\text{nsp}_{15})} \Delta \text{nsp}_{15} + \frac{\partial v_{\beta}}{\partial(\text{nsp}_{16})} \Delta \text{nsp}_{16}. \end{aligned} \quad (7)$$

where:

nsp₁ – degradation cellular mRNA [3];

nsp₂ – not well understood [4];

nsp₃, nsp₅ – cleaving polypeptides [5];

nsp₄, nsp₆ – formation DMV [6];

nsp₇, nsp₈, nsp₁₂ – DNA modification [7];

nsp₉ – dimerization RNA [8];

nsp₁₀, nsp₁₄ и nsp₁₆ – dsRNA sensors evasion [9];

nsp₁₁ – not well understood [4];

nsp₁₃ – RNA degradation [9];

nsp₁₅ – endoribonuclease [10].

The general destructive functions of the coronavirus strain 2019-nCoV can be described by function (7). Human safety from the influence of coronaviruses can be estimated by the formula (6).

4. Necessary and sufficient conditions for human infection with coronavirus

The necessary condition for the transition from one state to another of the HVE system is the presence of coronavirus (CoVs), and the reduced distance (x) to the source of danger (coronavirus), the spread of the epidemic (w) and exposure time (τ) are sufficient (table 1).

Table 1. Necessary and sufficient conditions for occurrence and the course of the infectious process in the body

State probability	Type of condition	Viral activity parameters
p_1	Safe condition (lack of necessary and sufficient conditions)	$C^1 = \begin{pmatrix} c < c^d \\ x > x^d \\ \tau < \tau^d \\ w < w^d \end{pmatrix}$
p_2	Dangerous state of exposure to the human immune system (there is the necessary (c), but there are no sufficient conditions)	$C^2 = \begin{pmatrix} c \geq c^d \\ x > x^d \\ \tau < \tau^d \\ w < w^d \end{pmatrix}$
p_3	Condition infection process in organism (presence of the necessary (c) and sufficient conditions (x, w))	$C^3 = \begin{pmatrix} c > c^d \\ x < x^d \\ \tau < \tau^d \\ w > w^d \end{pmatrix}$
p_4	The state of cell death (destruction of the nucleus and cell membrane) (presence of necessary (c) and sufficient conditions (x, τ, w))	$C^4 = \begin{pmatrix} c > c^d \\ x < x^d \\ \tau > \tau^d \\ w > w^d \end{pmatrix}$

Note - c^d, x^d, τ^d, w^d are the maximum permissible parameters for the spread of infection.

It is advisable to use semi-Markov processes characterized by arbitrary probability distribution functions p_i as a model of transition states of the HVE system. The transition of the system from the C_i state to the C_j state is carried out under the influence of viral activity with a transition probability λ_{ij} . The determination of the probability $p_i(t)$ of the state of the system is determined by solving the system of Kolmogorov equations

$$\frac{dp_i(t)}{dt} = \sum_{j=1}^n \lambda_{ij} p_j(t) - p_i(t) \sum_{j=1}^n \lambda_{ij}, \quad (i=1,2,3,\dots,n),$$

with initial conditions $p_1(0), p_2(0), \dots, p_n(0); \quad p_i(0) \geq 0, \quad \sum_{i=1}^n p_i(0) = 1.$

Based on this, the HVE system in terms of human safety for the disease can be in one of four states:

C_{HVE}^1 – a safe condition when the necessary conditions for the occurrence of a viral infection are absent in the HVE system;

C_{HVE}^2 – a condition of a dangerous situation when a viral infection exists in the HVE system, but there are no sufficient conditions for the defeat of the human coronavirus (the cell resists penetration into its virus, the weak virulence of the coronavirus);

C_{HVE}^3 – the state of the infectious process in the body when the coronavirus penetrated the cell and the reproduction of the coronavirus began;

C_{HVE}^4 – the state of cell death, characterized by the destruction of the cell membrane and cell nucleus.

The relationships between the probabilistic states of the HVE system are presented in Fig. 2, from which it can be seen that the HVE system can transition from a safe state (1) to a dangerous (2), infectious (3) state and vice versa, with an increase in the body's immune system, the cell does not allow penetration and reproduction of the coronavirus in it. The transition from the infectious state to the state of cell death (4) is final, since the cell is destroyed at this point in time. The system of differential equations for the probability graph of states p_i and transitions λ_{ij} of the HVE system is shown in Fig 2.

Figure 2. State probability graph p_i and transitions λ_{ij} the system HVE: safe (1), dangerous (2), infectious (3) and cell death (destruction) (4).

Formalization of the space of hazard parameters i CoVs allows us to assess the degree of safety of human infection:

$$\theta_i = \begin{cases} \frac{1}{4} \left(\frac{c_i^d - c_i}{c_i^d} + \frac{x_i - x_i^d}{x_i^d} + \frac{w_i^d - w_i}{w_i^d} + \frac{\tau_i^d - \tau_i}{\tau_i^d} \right), & \text{при } (c_i < c_i^d) \wedge (x_i > x_i^d) \wedge (w_i < w_i^d) \wedge (\tau_i < \tau_i^d); \\ 0, & \text{при } (c_i \geq c_i^d) \vee (x_i < x_i^d) \vee (\tau_i > \tau_i^d) \vee (w_i > w_i^d). \end{cases} \quad (8)$$

Thus, the general indicator for many sources of coronaviruses is calculated as the arithmetic mean or equal to zero if at least one of the sources of coronavirus is dangerous:

$$\Theta = \begin{cases} \frac{1}{N} \sum_{i=1}^N \theta_i, & \forall i = \overline{1, N} : \theta_i > 0; \\ 0, & \exists i = \overline{1, N} : \theta_i = 0. \end{cases} \quad (9)$$

Using equations (8) and (9), one can determine the epidemiological state in the studied region (city).

5. Statistical model of cell infection

Coronaviruses have some unique features in RNA transcription, protein composition, and assembly mechanisms. They penetrate the cell through adsorption endocytosis. After that, the attachment of genomic RNA to ribosomes occurs, which leads to the synthesis of viral RNA-dependent RNA polymerase. Upon transcription of genomic RNA, a complementary minus strand of RNA of full length is formed. Its synthesis is completed 5-6 hours after infection. We compile a statistical model of cell infection with respect to probabilistic function $\mathcal{G}(t)$.

In the course of human life, the parameters of the sources of infections (c , x , w and τ) of the HVE system can change both deterministically (for example, natural aging of the cell) and stochastically (under the influence of external influences, for example, viruses):

$$c = c(\mathcal{G}_c(t), t), \quad x = x(\mathcal{G}_x(t), t), \quad w = w(\mathcal{G}_w(t), t), \quad \tau = (\mathcal{G}_\tau(t), t), \quad (10)$$

where $\mathcal{G}(t)$ is a random event.

Differentiating complex functions (10), we obtain

$$\begin{aligned} \frac{dc(\mathcal{G}_c(t), t)}{dt} &= \frac{\partial c(\mathcal{G}_c(t))}{\partial \mathcal{G}_c(t)} \cdot \frac{d\mathcal{G}_c(t)}{dt} + \frac{\partial c(t)}{\partial t}, \\ \frac{dx(\mathcal{G}_x(t), t)}{dt} &= \frac{\partial x(\mathcal{G}_x(t))}{\partial \mathcal{G}_x(t)} \cdot \frac{d\mathcal{G}_x(t)}{dt} + \frac{\partial x(t)}{\partial t}, \end{aligned} \quad (11)$$

$$\frac{dw(\mathcal{G}_v(t), t)}{dt} = \frac{\partial w(\mathcal{G}_v(t))}{\partial \mathcal{G}_v(t)} \cdot \frac{d\mathcal{G}_v(t)}{dt} + \frac{\partial w(t)}{\partial t},$$

$$\frac{d\tau(\mathcal{G}_\tau(t), t)}{dt} = \frac{\partial \tau(\mathcal{G}_\tau(t))}{\partial \mathcal{G}_\tau(t)} \cdot \frac{d\mathcal{G}_\tau(t)}{dt} + \frac{\partial \tau(t)}{\partial t},$$

where $\frac{\partial c(\mathcal{G}_c(t))}{\partial \mathcal{G}_c(t)}, \frac{\partial x(\mathcal{G}_x(t))}{\partial \mathcal{G}_x(t)}, \frac{\partial w(\mathcal{G}_v(t))}{\partial \mathcal{G}_v(t)}, \frac{\partial \tau(\mathcal{G}_\tau(t))}{\partial \mathcal{G}_\tau(t)}$ – probability distribution density of a random value of cell infection;

$\frac{\partial c(t)}{\partial t}, \frac{\partial x(t)}{\partial t}, \frac{\partial w(t)}{\partial t}, \frac{\partial \tau(t)}{\partial t}$ – functions of deterministic change of coronavirus parameters;

$\frac{d\mathcal{G}_c(t)}{dt}, \frac{d\mathcal{G}_x(t)}{dt}, \frac{d\mathcal{G}_w(t)}{dt}, \frac{d\mathcal{G}_\tau(t)}{dt}$ – infection time distribution density.

In the case of the normal distribution law of a random variable with the exponential law of the time of cell destruction клетки we obtain the following expressions:

$$\begin{aligned} c(t) &= \int_0^t \frac{dc(\mathcal{G}_c(t), t)}{dt} dt = \int_0^t \left(\frac{1}{\sigma_c \sqrt{2\pi}} \exp\left(-\left[\frac{\mathcal{G}_c - M(\mathcal{G}_c)}{2\sigma_c}\right]^2\right) \exp(-\lambda_c t) \right) dt + \\ &+ \int_0^t \frac{dc(t)}{dt} dt = c(t) + \frac{1}{\sigma_c \sqrt{2\pi}} \exp\left(-\left[\frac{\mathcal{G}_c - M(\mathcal{G}_c)}{2\sigma_c}\right]^2\right) \exp(-\lambda_c t), \end{aligned} \quad (12)$$

$$x(t) = x(t) + \frac{1}{\sigma_x \sqrt{2\pi}} \exp\left(-\left[\frac{\mathcal{G}_x - M(\mathcal{G}_x)}{2\sigma_x}\right]^2\right) \exp(-\lambda_x t),$$

$$w(t) = w(t) + \frac{1}{\sigma_v \sqrt{2\pi}} \exp\left(-\left[\frac{\mathcal{G}_v - M(\mathcal{G}_w)}{2\sigma_w}\right]^2\right) \exp(-\lambda_w t),$$

$$\tau(t) = \tau(t) + \frac{1}{\sigma_\tau \sqrt{2\pi}} \exp\left(-\left[\frac{\mathcal{G}_\tau - M(\mathcal{G}_\tau)}{2\sigma_\tau}\right]^2\right) \exp(-\lambda_\tau t).$$

With the known laws of the distribution of a random variable using the system of equations (12), it is possible to determine the probability of infection of the cell in order to take timely measures to prevent the protection of the population.

6. Development of a system for protecting a person from coronavirus damage

Active methods are currently underway to develop a vaccine for the 2019-nCoV virus strain. Schematically depict the cell protection system shown in Fig. 3.

Figure 3. Model of a cell protection system: L - protection system.

Protection L should ensure that exposure to hazardous factors of coronaviruses is not higher than the permissible values

$$L_c \cdot c(t), L_x \cdot x(t), L_v \cdot v(t), L_\tau \cdot \tau(t), \quad (13)$$

where: L_c – Protection by virus intensity, L_x – Distance protection, L_t – Exposure time protection.

The safety of the HVE system according to the parameters of the danger source of coronaviruses will be ensured in case of inequalities:

$$c^d - L_c \cdot c(t) \geq 0, L_x \cdot x(t) - x^d \geq 0, v^d - L_v \cdot v(t) \geq 0, \tau^d - L_\tau \cdot \tau(t) \geq 0. \quad (14)$$

The safety assessment of the HVE system according to the i -th source of danger of the coronavirus, taking into account the protection factors, will be determined by the expression (13) taking into account inequalities (14)

$$\theta_i = \frac{1}{4} \left[\left(\frac{c_i^d - L_{ci} \cdot c_i(t)}{c_i^d} \right) + \left(\frac{L_{xi} x_i(t) - x_i^d}{x_i^d} \right) + \left(\frac{w_i^d - L_{vi} \cdot w_i(t)}{w_i^d} \right) + \left(\frac{\tau_i^d - L_{ti} \cdot \tau_i(t)}{\tau_i^d} \right) \right].$$

Protection L should ensure that the exposure to hazardous factors of the coronavirus is not higher than the permissible values; it can be defined as means and measures to combat coronavirus that reduce the parameter values to acceptable values

$$L_x \geq \frac{\theta_i^d}{\theta_i}, \quad L_w \leq \frac{\theta_i^d}{\theta_i}, \quad L_c \leq \frac{\theta_i^d}{\theta_i}, \quad L_\tau \leq \frac{\theta_i^d}{\theta_i},$$

where θ_i^d is the permissible value of the source of the viral hazard.

The development and implementation of this model will allow timely and reliable monitoring of the epidemiological state of the HVE system from the influence of coronaviruses.

7. Conclusion

A methodology for instrumental assessment of the state of the Human-Virus-Environment (HVE) system based on structural and functional analysis has been developed, which allows calculating the development models of the coronavirus epidemic of strain 2019-nCoV taking into account the destructive characteristics of human cells from unstructured proteins. Scientific and practical value lies in the generalization of the evaluation criteria for monitoring the safe state of the HVE system, based on the methods of the general theory of systems and implementing instrumental approaches to identifying and managing the protective properties of the HVE system.

8. Research Methods

In substantiating the methods and algorithms of human protection, we used methods of system analysis, general systems theory, differential and integral calculus, methods of mathematical modeling, mathematical statistics and probability theory, as well as methods of epidemiology, immunology and virology. Research methods included an analysis of the epidemiological situation of coronaviruses in the world.

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Figures

$H = \{h_1, h_2, \dots, h_l\}$ – many types of people;

$V = \{v_1, v_2, \dots, v_n\}$ – coronavirus family;

$E = \{e_1, e_2, \dots, e_m\}$ – many environmental elements;

$U = \{u_1, u_2, \dots, u_l\}$ – many controls.

Figure 1

The relationship of the elements of the studied HVE system.

$$\frac{dp_1(t)}{dt} = \lambda_{21} p_2(t) - \lambda_{12} p_1(t)$$

$$\frac{dp_2(t)}{dt} = \lambda_{12} p_1(t) + \lambda_{32} p_3(t) - \lambda_{21} p_2(t) - \lambda_{23} p_2(t)$$

$$\frac{dp_3(t)}{dt} = \lambda_{23} p_2(t) - \lambda_{32} p_3(t) - \lambda_{34} p_3(t)$$

$$\frac{dp_4(t)}{dt} = \lambda_{34} p_3(t)$$

Figure 2

State probability graph p_i and transitions λ_{ij} the system HVE: safe (1), dangerous (2), infectious (3) and cell death (destruction) (4).

Figure 3

Model of a cell protection system: L - protection system.