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Mathematical Modeling of Antitumor Viral Vaccine Therapy: From the Experiment to the Clinic

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Abstract: The paper presents the model developed to identify efficient strategies of antitumor viral vaccine introduction. These strategies are able to produce complete suppression of the tumor growth. The model was developed in MatLab-Simulink. Three efficient strategies of viral vaccine introduction were produced. It was found that the choice of the strategy depends on the tumor size at the start of the treatment, and the range of the tumor sizes for each of the strategies was identified. For the small tumors, elimination of the tumor can be achieved through single-shot vaccine administration in dosages that lead to the death of tumor cells caused directly by the virus. For the big tumors that are within the threshold size, elimination of the tumor can be achieved through repeated vaccine administrations with stepwise reduction of time periods between them. For the tumors of any size, the strategy of repeated administration of the virus-based vaccine that allows stabilizing the tumor size as per the start of the treatment was defined.

Keywords: mathematical model, experimental oncology, tumor cells, kinetic growth curves, vaccine therapy, virus, immune response, antibodies, allometric proportions

1. INTRODUCTION

Effective treatment of cancer remains one of the key challenges of contemporary healthcare. Addressing this challenge requires extensive research based on experimental studies that are further translated into clinic. One of the promising directions for combating oncological diseases is the development of different treatment methods within the domain of immunotherapy. Cancer immunotherapy research by J. Allison and T. Honjo was awarded 2018 Nobel Prize in Medicine.

Significant progress in cancer treatment was produced by breakthroughs in molecular biology and immunology that made it possible to understand the reasons behind tumor degeneration and the development of tumor process [1-3]. Immune system can resist the emergence and development of the tumor process, and the aim of immunotherapy is to stimulate the immune system to fight against the tumor cells. There are two ways to stimulate the immune system: specific and non-specific. *Specific* antitumor vaccines are based on dendritic cells that carry the information on the antigens specific for each type of tumor [4-8]. *Non-specific* virus-based antitumor vaccines can induce the immune response against the tumor by producing new protein formations on the surface of the tumor cells [9-13]. Such vaccines are based on the viruses that are not dangerous for the humans but are able to identify and destroy the tumor cells [14-17].

The virus is able to induce the process of tumor cells' death that has two stages. The first stage is produced by the virus itself. Settling down on the tumor cell, the virus penetrates

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inside, multiplies itself and destroys the cell. Meanwhile the immune system reacts at the virus intrusion and destroys it together with the tumor cell.

The second stage of the tumor cells' death evolves later, due to the immune system's reaction to the population of infected tumor cells. When settling down on the surface of the cells, the virus leaves specific protein formations on the membrane surface. This produces a population of infected tumor cells that are detected by immune system as foreign. In response, immune system produces antibodies that destroy the infected tumor cells [17-19]. Thus the virus acts as a specific marker of the tumor cells and helps to overcome the irresponsiveness of the immune system against uninfected tumor cells.

One of the key advantages of immunotherapy is the absence of toxic effects associated with chemotherapy and radiation therapy. Since there is no need for additional treatment to mitigate the negative side effects, this makes immunotherapy a more harmless and cost-effective method as compared to other approaches to cancer treatment. Low toxicity makes it possible to expand the range of dosages – however, this requires additional experimental studies and therefore implies higher research costs. Computational experiments based on the mathematical model of vaccine therapy make it possible to define the optimal dosages, assess the effectiveness of immune response depending on the vaccine dosage, and describe the dynamics of the tumor process for different treatment strategies. Data obtained through computational experiments may be used to define optimal treatment strategies that produce complete tumor regression.

Given the high costs of experimental and clinical studies, computational experiments based on mathematical models can produce a lot of useful information based on the limited amount of experimental data. Modelling makes it possible to expand the study of the range of applicable dosages and treatment strategies when exploring the new methods of antitumor therapy, thus reducing time and labor costs and the number of animals required for conducting an experiment in vivo. Moreover, research in molecular biology, cell biology, biophysics and immunology has produced a large amount of data that also require processing and analysis with the use of specialized computer technologies based on mathematical modelling [8-11]. However, despite its advantages, modelling is still not widely used in experimental and clinical oncology. This paper aims to demonstrate that computational experiments based on mathematical modelling may produce meaningful results for defining cancer treatment strategies, complementing in vivo experimental approaches and enabling more efficient translation of experimental results to the clinic, building on the study published in Mathematical Biology & Bioinformatics earlier in 2019 [19].

2. PROBLEM STATEMENT

This study aims to develop an algorithm for finding strategies for the use of antitumor viral vaccine to completely suppress tumor growth. To achieve this aim, a software package was developed in the MatLab-Simulink system, which includes several mathematical models:

- mathematical model of vaccine therapy, describing the mechanism of tumor cell death as a result of the immune response to the injection of the virus [10,18,19],
- mathematical model of infectious disease by G. I. Marchuk, describing the dynamics of the formation of antibodies against the virus by the immune system [20-22],
- mathematical model by H. F. Skipper, describing how the proportion of the fast proliferating tumor cells decreases in the growing tumor [10,23],
- mathematical model of antitumor therapy with discontinuous trajectories, evaluating the effectiveness of therapeutic effects on the experimental trajectories of tumor growth after the injection of a viral vaccine [10,18,19].

The values of the parameters of the complex mathematical models are given in the table 1 [19, p. 44].

The complexity and nonlinearity of differential equations of mathematical models does

not allow to obtain the solution analytically without the use of computational software. On the basis of the developed software package, a computational experiment was conducted, which allowed to investigate the effectiveness of various strategies for the injection of viral vaccines depending on the dose and size of the tumor at the time of its injection.

3. MATHEMATICAL MODEL OF VACCINE THERAPY WITH VIRUS VAL

The mathematical model of vaccine therapy describes the mechanism of tumor cells' death under the influence of two factors – the virus itself and antibodies against infected tumor cells, on the basis of experimental data on the growth of Erlich tumor in experimental animals after a single administration of the vaccine with Venezuelan equine encephalitis (VEE) virus [17].

The experiments were carried out on 2-month-old female mice of the line BALB/c, C57B1/6 and DBA/2. In total, 690 animals were used in the experiments [17].

The process of tumor cell growth without treatment (control) is described by a simple differential equation [19, p. 38]:

$$\frac{dN(t)}{dt} = \lambda(t) \cdot N(t), \text{ with } N(t_0) = N_0, \tag{1}$$

where $N(t)$ is the number of tumor cells, t denotes time, $\lambda(t)$ is the parameter characterizing the growth rate of tumor cells, N_0 is the initial number of tumor cells at time $t = 0$.

The type of function describing tumor growth without treatment was determined by experimental curves of Erlich adenocarcinoma growth by regression analysis in MatLab (Fig. 1). The experimental curve of tumor growth without treatment is most accurately described by the Gompertz function, which is the solution of the differential equation (1) for $\lambda(t) = \alpha_N \beta_N \exp(-\beta_N t)$.

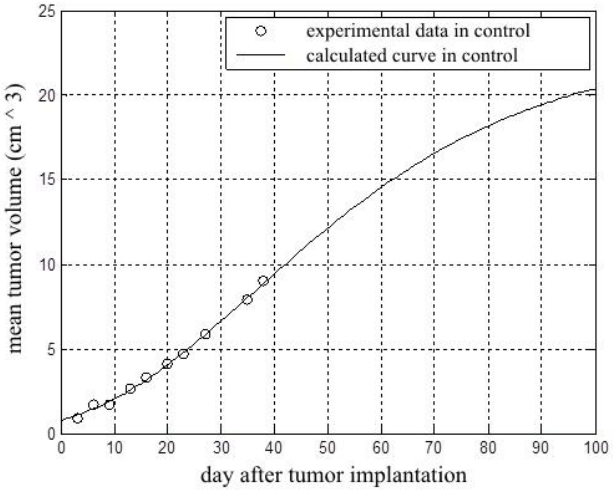


Fig. 1. Approximation of experimental data on the growth of Ehrlich adenocarcinoma in control by the Gompertz function

The Gompertz function is:

$$N(t) = N_\infty \exp(-\alpha_N \cdot \exp(-\beta_N t)) = N_0 \exp(\alpha_N (1 - \beta_N \exp(-\beta_N t)), \tag{2}$$

where $N_\infty = N_0 \exp(\alpha_N)$ is the maximum tumor size for $t \to \infty$.

Calculated values of the parameters of the Gompertz function and the sum of squared deviations (SKO = 0.21) are shown in Table 1 [19, p. 44].

Analysis of experimental data on tumor growth after the introduction of a viral vaccine (Fig. 2, lower curve) allows us to distinguish two periods of intensive death of tumor cells.

The first period lasts from 6 to 8 days, and the second from 13 to 16 days. We can assume that the first stage is associated with the reaction of the immune system to the virus and the formation of antibodies specific to this virus. And the second stage is associated with the appearance of dead tumor cells infected with a virus, and the formation of antibodies specific to these tumor cells [15-17].

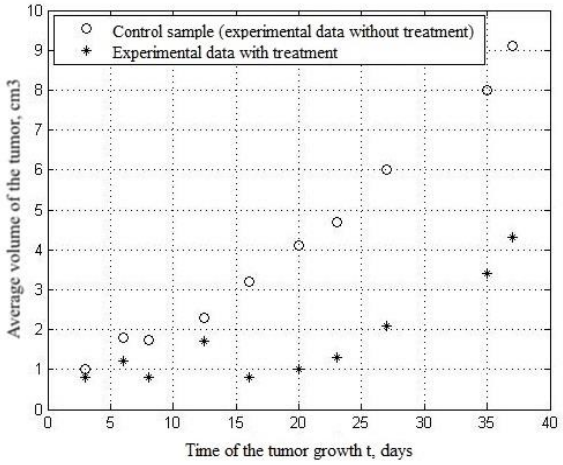


Fig. 2. Experimental data on the growth of Ehrlich adenocarcinoma without treatment and after a single injection of the vaccine [17-19]

As a result of the interaction of the virus with tumor cells, three populations of tumor cells emerge (Fig. 3).

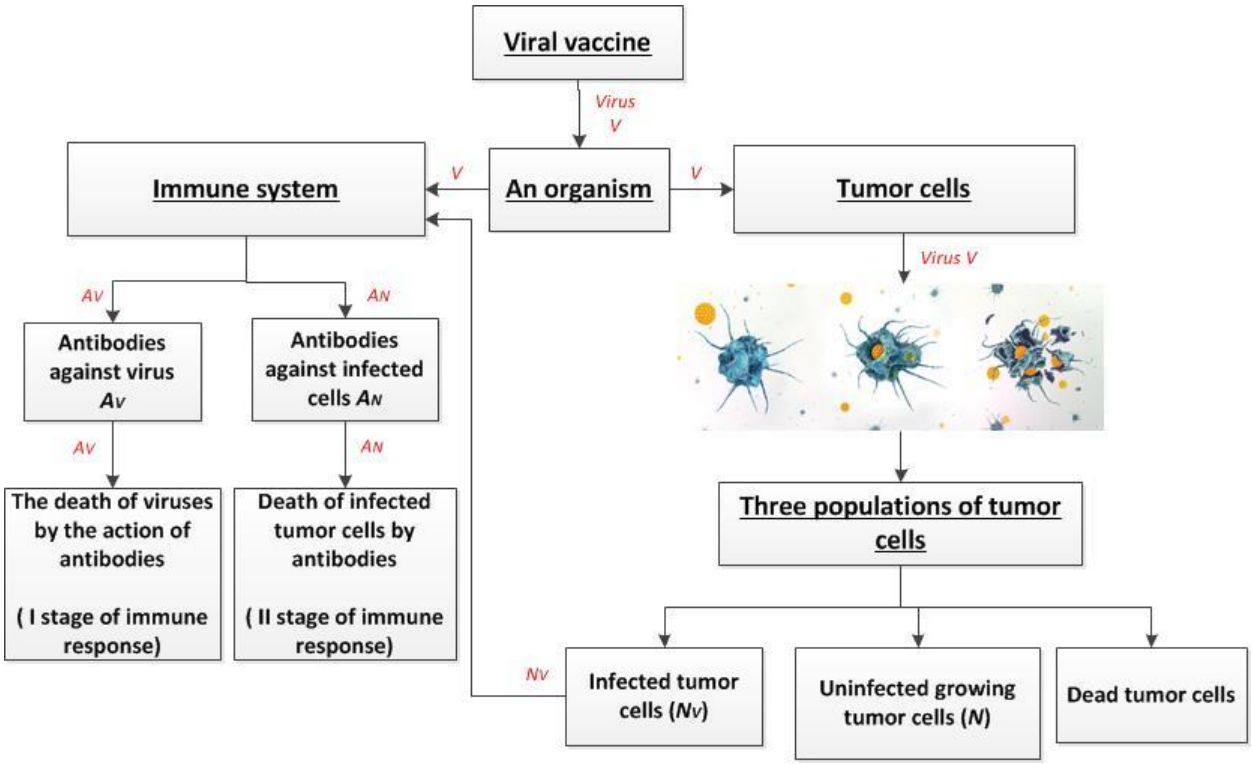


Fig. 3. Interaction of the virus with tumor cells and immune system

The population of tumor cells carrying the virus is part of the tumor cells on which the virus is absorbed. Penetrating inside the cell and multiplying there, the virus makes the tumor cell die.

The population of infected tumor cells has specific protein formations on the cell membrane which are perceived as alien by the immune system. Thus this population dies under the action of the antibodies produced by the immune system.

The population of uninfected tumor cells remains alive and is capable of multiplying and resuming tumor growth.

A mathematical model of vaccine therapy describing the dynamics of two-stage tumor cell death is presented in the form of a system of differential equations (1–10) [18–20].

The dynamics of tumor growth before the introduction of the vaccine is described by a differential equation of the form:

$$\frac{dN(t)}{dt} = \lambda(t)N(t), \quad t \in [0, t_V], \text{ with } N_0 = N(t_0), \tag{3}$$

where $N(t)$ is the population of tumor cells before administration of the vaccine,

$t_V = \tau_1 + Z_{CV}$ is the beginning of the immune response against viruses.

τ_1 is the moment of injection of the vaccine,

Z_{CV} is the period of the delay of immune response against the virus.

The dynamics of growth and death of infected tumor cells after the introduction of the virus is described by the differential equation of the form:

$$\frac{dN_V(t)}{dt} = [\lambda(t) - K_V V(t) - K_{AV} A_V(t)] \cdot N_V(t), \quad t \in (t_V, t_N], \text{ with } N_{V0} = N(t_V) \tag{4}$$

where $N_V(t)$ is the population of infected tumor cells following injection of the vaccine,

$V(t)$ is the number of viruses,

$A_V(t)$ is the number of antibodies against the virus,

K_V is the coefficient of the rate of reproduction of the virus in a tumor cell,

K_{AV} is the coefficient of the rate of death of viruses as a result of interaction with antibodies $A_V(t)$.

The dynamics of growth and death of infected tumor cells under the action of antibodies at the second stage is described by the differential equation of the form:

$$\frac{dN_V(t)}{dt} = [\lambda(t) - K_{AN} A_N(t)] \cdot N_V(t), \quad t \in [t_N, t_L], \text{ with } N_{V0} = N(t_N), \tag{5}$$

where $t_N = \tau_1 + Z_{CN}$ is the moment of the immune response against infected tumor cells,

Z_{CN} is the delay time of the immune response against infected tumor cells,

$A_N(t)$ is the number of antibodies against infected tumor cells,

K_{AN} is the dimensional coefficient.

The death of tumor cells at each of the two stages occurs as a result of the development of the body's immune response to the introduction of a viral vaccine.

The first stage is associated with the formation of antibodies against the virus $A_V(t)$, and the second stage is associated with the formation of antibodies against infected tumor cells $A_N(t)$.

Graphs of antibody formation dynamics $A_V(t)$ against the virus and against infected tumor cells $A_N(t)$ are shown in Fig. 4 [19, p. 39].

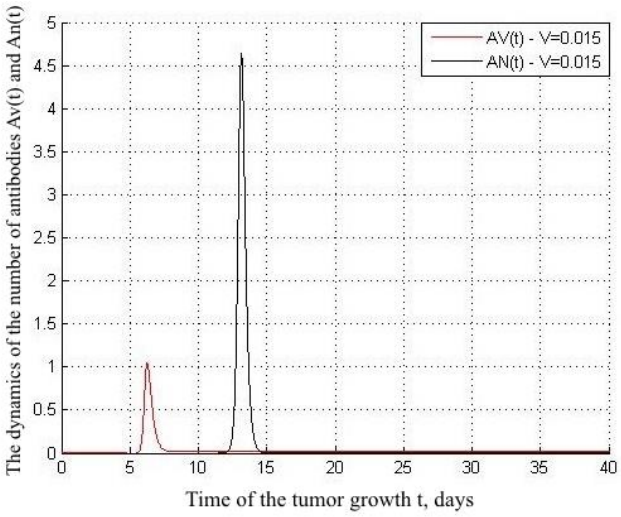


Fig. 4. Graph of the dynamics of the number of antibodies against the virus $A_V(t)$ (the first stage of the immune response) and against infected tumor cells $A_N(t)$ (the second stage of the immune response)) for the experimental dose $V_0 = 0.015$ on τ_1 = 1day

The mechanism of their formation is calculated on the basis of the model of infectious disease by G. I. Marchuk [20-22]. The parameters of this model are adapted for experimental curves of tumor growth after the introduction of viral vaccines.

The dynamics of the number of viruses according to the mathematical model of an infectious disease [20, 22] is described by the equation of the form:

$$\frac{dV(t)}{dt} = \alpha_V V(t) - \beta_V A_V(t) V(t), \tag{6}$$

where $V_0 = V(\tau_1)$ is the initial dose of virus vaccine, τ_1 is the moment of the first introduction of a viral vaccine, α_V is the rate of reproduction of the virus inside the cell, β_V is the rate of death of viruses in their interaction with antibodies $A_V(t)$ [19, p. 39].

The initial condition for the solution of equation (4) is taken as a control parameter characterizing the introduced dose of the viral vaccine $V_0 = V(\tau_1)$.

The first stage of the body's immune response to the introduction of the virus is determined by the number of antibodies $A_V(t)$, which is calculated from the following equations:

$$\frac{dA_V(t)}{dt} = \alpha_A C_V(t - t_V) - \beta_{AV} A_V(t) V(t) - \beta_V A_V(t), \tag{7}$$

where α_A is the rate of formation of antibodies from one plasma cell, β_{AV} is the rate of loss of antibodies due to the interaction with viruses $A_V(t)$, β_V is the rate of reduction of the number of antibodies due to natural destruction, $t_V = \tau_1 + Z_{CV}$ is the moment of the beginning of immune response against viruses [19, p. 40].

Due to the fact that the time of virus reproduction in the experimental tumor was not recorded in the available experimental data [15-17], when constructing the model, it was assumed that the period of virus reproduction inside the tumor cell, leading to its death, can be considered with sufficient accuracy equal to the time of delay of the immune response against the virus Z_{CV}. Then in equations (7) and (8) the time of introduction of the virus was taken into account as a parameter $t_V = \tau_1 + Z_{CV}$, which records the moment of the beginning of the immune response against viruses.

Number of plasma cells $C_V(t)$ is determined from the equation:

$$\frac{dC_V(t)}{dt} = \alpha_C V(t-t_V) Av(t-t_V) - \beta_{CV}\left[C_V(t) - C_{VN}\right], \text{ with } C_V(t_V) = C_{VN}, \quad (8)$$

where α_C is the rate of formation of plasma cells, β_{CV} is the constant coefficient, Z_{CV} is the period of delay in the development of antibodies against the virus (first stage of immune response). The second term of this equation reflects the maintenance of the initial number of plasma cells in the norm C_{VN} [19, p. 40].

The second stage of the immune response of the body to the formed infected tumor cells was determined by the number of antibodies, which was calculated from the following equations:

$$\frac{dA_N(t)}{dt} = \alpha_{AN} C_N(t-t_N) - \beta_{AN} A_N(t) N_V(t) - \beta_{NN} A_N(t), \quad (9)$$

where α_{AN} is the rate of formation of antibodies, β_{AN} is the coefficient that describes the rate of reduction of the number of antibodies $A_N(t)$ due to their interaction with infected tumor cells $N_V(t)$, β_{NN} is the rate of reduction of the number of antibodies due to natural destruction [19, p. 40].

Number of plasma cells $C_N(t)$ is determined from the equation:

$$\frac{dC_N(t)}{dt} = \alpha_{CN} N_V(t-t_N) A_N(t-t_N) - \beta_{CN}\left[C_N(t) - C_{NN}\right], \text{ with } C_N(t_N) = C_{NN}, \quad (10)$$

where α_{CN} is the rate of formation of plasma cells, β_{CN} is the constant coefficient, Z_{CN} is the period of delay in the development of antibodies against the infected tumor cells (second stage of immune response), C_{NN} is the initial number of plasma cells in the norm [19, p. 40].

To adequately describe the effectiveness of viral vaccines, it is necessary to take into account that one of the factors of high selectivity of viruses in relation to tumor cells is the high rate of their division in comparison with normal body tissues [4-7]. The measured tumor volume contains fractions of rapidly and slowly proliferating tumor cells, which is described in detail in the mathematical model of tumor growth by Skipper [23]. As the size of the tumor increases, the fraction of rapidly dividing tumor cells decreases, while the fraction of slowly dividing cells and temporarily non-dividing cells increases.

To describe how the tumor size is related to the efficiency of the vaccine, $P(t_N)$ function is included in the model. This function describes the dynamics of the decline in the share of rapidly proliferating cells with increasing size of the tumor [19]:

$$P(t) = 1 - \left[\frac{1}{\pi K_p} arctg\left(\frac{2\alpha_p \beta_p \cdot t}{1-\beta_p^2 \cdot t^2}\right)\right], \quad (11)$$

where α_p and K_p are constant parameters, t denotes time (in days), $\beta_p = 1/t^*$, where t^* is the moment when numbers of the rapidly and slowly proliferating cells are equal [19, p. 41].

Then the number of infected cells in the measured tumor volume is calculated as $N_V(t_N) = N(t_N)P(t_N)$, where $t_N = \tau_1 + Z_{CN}$ is the moment when the immune response against infected tumor cells begins.

As a result of the interaction of the virus with tumor cells, three populations of tumor

cells develop in the tumor volume $N_V(t)$ (Fig. 5) [19, p. 41].

The structure of the equations of the model is such that the existence, uniqueness and nonnegativity of solutions in this work under nonnegative initial conditions are satisfied, which was proved and stated in the work of N. V. Pertsev [21, p. 156-157].

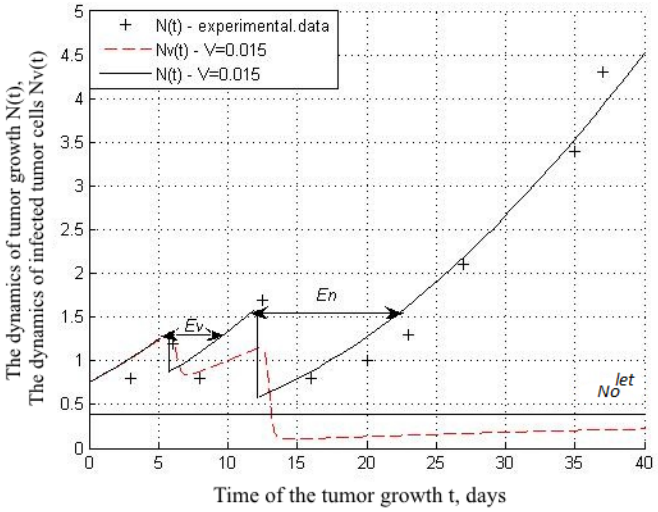


Fig. 5. Calculation curves of the dynamics of infected cells $N_V(t)$ (dotted line) and the kinetic trajectory of tumor growth $N(t)$ after dose injection $V_0 = 0.015$ at $\tau_1 = 1$ day, ε_V and ε_N are duration of the delay tumor growth after each stage of tumor cells' death. Experimental data is denoted by +

Figure 5 shows two calculated curves. The dotted line describes the dynamics of growth and death of infected tumor cells in accordance with the model of vaccine therapy (1) – (11). The solid line shows the dynamics of the number of surviving tumor cells after the first stage and the second stage of immune response in accordance with the mathematical model of anticancer therapy with discontinuous trajectories [19].

4. A MATHEMATICAL MODEL OF ANTICANCER THERAPY WITH DISCONTINUOUS TRAJECTORIES TO PREDICT THE DYNAMICS OF TUMOR GROWTH

When constructing a mathematical model of antitumor therapy with discontinuous trajectories, several assumptions were made to describe the death and subsequent growth of the experimental tumor [10, 18].

1. Tumor growth without the introduction of a viral vaccine (control) and after its introduction is described by the Gompertz function with the preservation of the values of the parameters of the function.

2. The death of tumor cells occurs instantly, causing a sudden decrease in the size of the tumor at the beginning of the immune response at each stage of cell death.

3. The trajectory of tumor growth after the death of tumor cells is shifted in time for the duration of the delay in tumor growth $\varepsilon(V_0)$ after each stage of their death.

4. Duration of tumor growth delay $\varepsilon(V_0)$ is the time interval between the start of immune response (i.e. when the number of tumor cells starts to decline affected first by the virus at t_V and then by the antibodies at t_N) and the moment when the tumor, resuming its growth, reaches the same size as at t_V and t_N respectively [10, 18].

The mathematical model of anticancer therapy with discontinuous trajectories is used to construct dynamic trajectories of tumor growth after two-stage death of tumor cells after the

introduction of a viral vaccine (Fig. 5 – $N(t)$) [19, p. 41].

The dynamics of tumor growth before the injection of the vaccine is described by a differential equation (12), which is similar to the equation of tumor growth in the control (1):

$$\frac{dN(t)}{dt} = \lambda(t)N(t), \quad t \in [0, t_V], \text{ with } N_0 = N(t_0), \tag{12}$$

where $N(t)$ is the size of the tumor before vaccine injection,

$\lambda(t) = \alpha_N \beta_N \exp(-\beta_N t)$ is tumor growth rate in control,

$t_V = \tau_1 + Z_{CV}$ is the moment when tumor cells start to die in response to the virus (1st stage of immune response),

τ_1 is the moment of vaccine injection,

Z_{CV} is the period of delay of the immune response against the virus.

The dynamics of tumor growth after the first stage of tumor death is described by a differential equation of the form:

$$\frac{dN(t)}{dt} = \lambda(t - t_V)N(t - \varepsilon_V), \; t \in [t_V, t_N], \text{ with } N^R(t_V) = N(t_V)S_V(t_V)\delta(t - t_V) \tag{13}$$

where $\delta(t - t_V)$ is pulsed Dirac function, describing the instantaneous death of tumor cells in the first stage of the immune response,

$S_V(t_V)$ denotes the proportion of dying tumor cells infected with the virus at the first stage of the immune response, which is determined from the equation:

$$S_V(t_V) = \frac{\Delta N_V(t_V)}{N_V(t_V)} \tag{14}$$

where $N_V(t_V)$ denotes the population of infected tumor cells at the start of the immune response,

$\Delta N_V(t_V)$ is the number of dying tumor cells in the first stage of the immune response, which is calculated as the difference between the maximum and minimum number of infected cells in the period from the beginning to the end of the 1st stage of immune response according to the equation:

$$\Delta N_V(t_V) = Nv(t_1^V) - Nv(t_2^V) \tag{15}$$

where t_1^V and t_2^V are the moments when the number of infected cells during the 1st stage of the immune response against the virus reaches maximal and minimal level (Fig. 5, dotted line),

$N^R(t_V)$ is the number of remaining tumor cells that continue to produce tumor growth, which is calculated from the equation:

$$N^R(t_V) = N(t_V) - \Delta N_V(t_V) \tag{16}$$

The trajectory of tumor growth after the first stage of tumor cell death is described by the Gompertz equations with a time shift for the duration of tumor growth delay (Fig. 5):

$$N(t - t_V) = N_0 \exp(\alpha_N(1 - \exp(-\beta_N(t_V - \varepsilon_V(V_0))))), \tag{17}$$

where $\varepsilon_V(V_0, t_V)$ is the delay in tumor growth after the first stage of the immune response.

The dynamics of tumor growth after the second stage of tumor cells' death is described

by the differential equation of the form:

$$\frac{dN(t)}{dt} = \lambda(t - t_N)N(t - \varepsilon_N), t \in [t_N, t_L], \text{ with } N^R(t_N) = N(t_V)S_N(t_N)\delta(t - t_N) \quad (18)$$

where $t_N = \tau_1 + Z_{CN}$ is the moment when the immune response against virus-infected tumor cells begins,

Z_{CN} is the period of delay of immune response against virus-infected tumor cells,

$\delta(t - t_N)$ is the pulsed Dirac function, describing the instantaneous death of tumor cells in the second stage of the immune response,

$S_N(t_N)$ is the proportion of dying tumor cells infected with the virus at the second stage of the immune response, which is determined from the equation:

$$S_N(t_N) = \frac{\Delta N_V(t_N)}{N(t_N)}, \quad (19)$$

$\Delta N_V(t_N)$ denotes the number of dying tumor cells in the second stage of the immune response. It is calculated as the difference between the maximum and minimum number of infected cells in the period from the beginning to the end of the 2nd stage of immune response according to the equation:

$$\Delta N_V(t_N) = N_V(t_1^N) - N_V(t_2^N), \quad (20)$$

where t_1^N and t_2^N are the moments when the number of infected cells during the 2nd stage of immune response against the virus reaches maximal and minimal level (Fig. 5, dotted line),

$N^R(t_N)$ is the number of remaining tumor cells that continue to produce tumor growth, which is calculated from the equation:

$$N^R(t_N) = N(t_N) - \Delta N_V(t_N) \quad (21)$$

Then the trajectory of tumor growth after the second stage of tumor cell death is described by the Gompertz equation with a time shift for the duration of tumor growth delay (Fig. 5):

$$N(t - t_N) = N_0 \exp(\alpha_N(1 - \exp(-\beta_N(t_N - \varepsilon_N(V_0))))) \quad (22)$$

where $\varepsilon_N(V_0)$ is the delay in tumor growth after cells' death in the second stage of the immune response.

The duration of the delay of tumor growth $\varepsilon_V(V_0)$ and $\varepsilon_N(V_0)$ was determined as the time interval between the start of immune response (i.e. when the number of tumor cells starts to decline affected first by the virus at t_V and then by the antibodies at t_N) and the moment when the tumor, resuming its growth, reaches the same size as at t_V and t_N respectively. Therefore:

$$N(t_V) = N(t_V + \varepsilon_V(V_0)), \quad (23)$$

$$N(t_N) = N(t_N + \varepsilon_N(V_0)). \quad (24)$$

The values of the parameters of the vaccine therapy model and the model of anticancer therapy with discontinuous trajectories are given in Appendix 1.

5. FINDING EFFECTIVE STRATEGIES OF VIRAL VACCINE INTRODUCTION

Evaluation of the effectiveness of various strategies of tumor growth after the injection of the viral vaccine was carried out on the basis of a mathematical model of anticancer therapy with discontinuous trajectories according to the equations (12) - (24).

The aim of efficient strategy is to reduce the number of tumor cells below the lethality threshold. In this case tumor will not be able to resume its growth. This threshold is denoted N_0^{let}. If the number of surviving cells is below the threshold after the first stage of immune response ($N^R(t_V) < N_0^{let}$) or after the second stage of the immune response ($N^R(t_N) < N_0^{let}$), this is interpreted in the model as the complete destruction of tumor cells. In this case, the life expectancy of treated animals will be equal to the average life expectancy of experimental animals without tumors T_L = 3 years.

5.1. Strategy of stabilization of tumor growth with multiple injection of the viral vaccine

Modeling of multiple injections of a viral vaccine within the framework of the constructed model allowed us to determine the algorithm for finding a strategy for stabilizing tumor growth with multiple injections of a constant dose of a viral vaccine V_0^{stab} (τ_1).

Results indicate that the strategy of stabilization is possible for a narrow range of dosage. This dosage should be able to produce an equal number of antibodies at each of the two stages of the immune response $A_V(V_0^{\text{stab}}, \tau_1) = A_N(V_0^{\text{stab}}, \tau_1)$ (Fig. 6, a,b) and (Fig. 7, a,b).

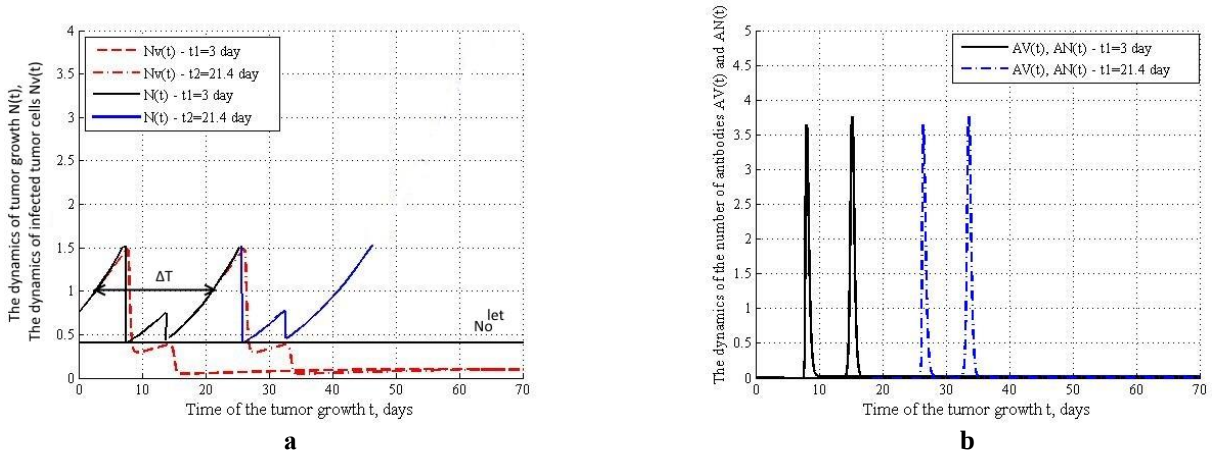
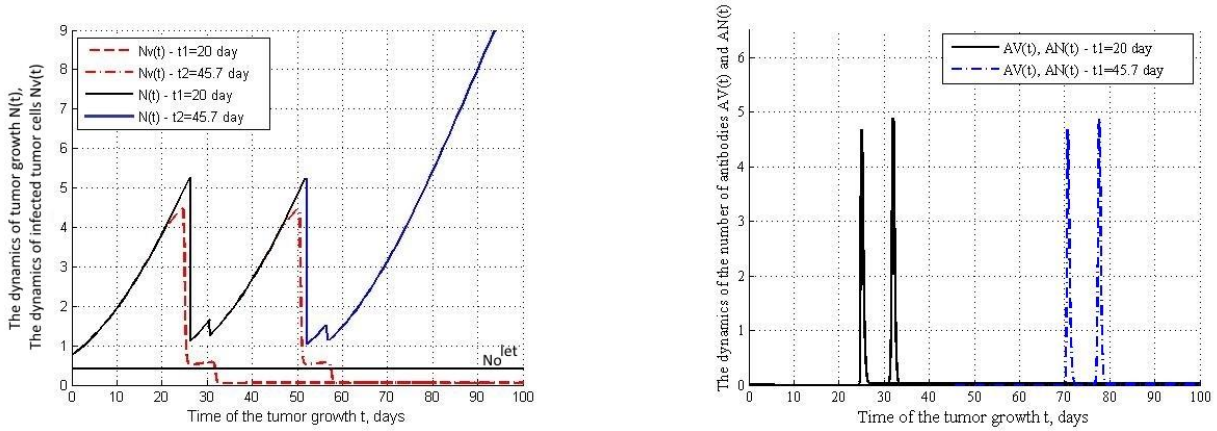


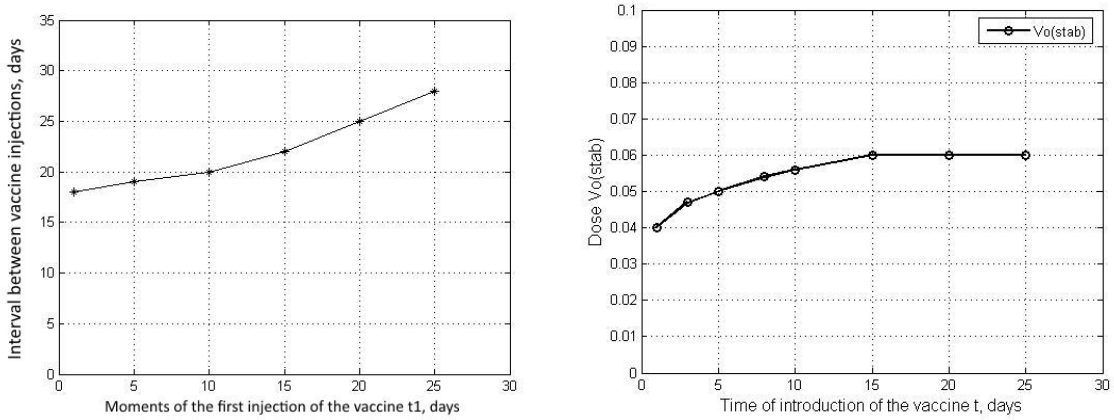
Fig. 6. Strategy to stabilize the tumor size with the injection of a viral vaccine on τ_1 = 3 days with an interval between injections ΔT = 18.4 days: **a** shows the trajectories of growth and death of tumor cells; **b** shows the dynamics of antibody formation $A_V(V_0, \tau_1)$ at the 1st and $A_N(V_0, \tau_1)$ at the 2nd stage of immune response



a **b**

Fig. 7. Strategy to stabilize the tumor size with the injection of a viral vaccine on $\tau_1 = 20$ days with an interval between injections $\Delta T = 25.7$ days: **a** shows the trajectories of growth and death of tumor cells; **b** shows the dynamics of antibody formation $A_V(V_0, \tau_1)$ at the 1st and $A_N(V_0, \tau_1)$ at the 2nd stage of immune response

The strategy of tumor growth stabilization is performed in the range of doses from V_0^{stab}=0.04 to V_0^{stab}=0.06 (Fig. 8,b) at a constant value of the duration of the interval between administration of the vaccine. Duration of intervals between repeated introductions of the vaccine ΔT increases with the size of the tumor (Fig. 8,a).



a **b**

Fig. 8. The dependence of the values of the parameters under the strategy of stabilization of tumor growth on the size of the tumor at the beginning of treatment: **a** shows the intervals between vaccine introductions $\Delta T(V_0^{\text{stab}}, \tau_1)$ **,** **b** shows the value of the introduced dose $V_0^{\text{stab}}(\tau_1)$

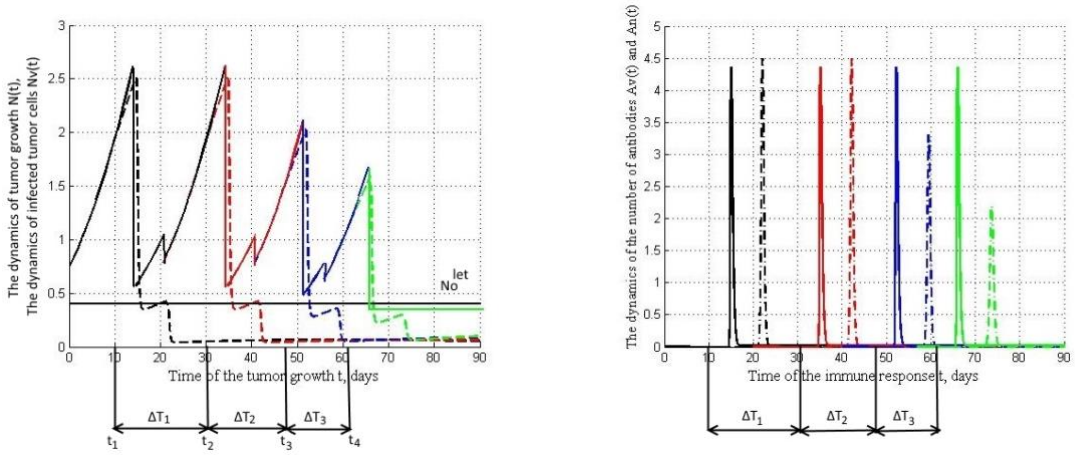
This strategy requires sufficiently large dosage which will be able to produce equally big number of antibodies at the 1st and the 2nd stages of immune response. Thus, this strategy allows to transfer the course of the disease into a chronic state by restraining the growth of the tumor. Within the framework of the constructed model, it is shown that it is possible to restrain the growth of a tumor of any size for an unlimited time. However, if vaccine is not introduced any longer, the tumor growth could resume.

The strategy of tumor growth stabilization is similar to the effect of inoculation from own tumor cells in the period between two successive injections of the vaccine.

5.2. Strategy of tumor growth suppression with multiple injection of the viral vaccine

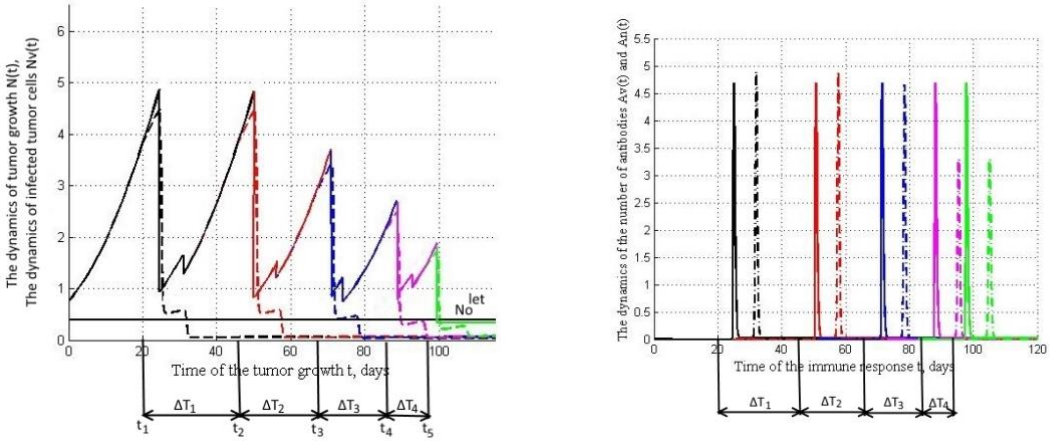
To solve the problem of reducing the number of tumor cells below the lethality threshold with repeated injection of the vaccine for all tumor sizes, agorhythm was developed, based on the strategy of stabilizing tumor growth, in which the duration of intervals between repeated injections of the viral vaccine was reduced step by step.

Figures 9,a and 10,a show the trajectories of tumor growth when the vaccine is injected 3 and 4 times, and the time intervals between consecutive injections are reduced. This allows to drive the number of tumor cells below the lethality threshold.



a **b**

Fig. 9. The strategy for multiple injection of the vaccine by reducing the interval between the doses V_0 = 0,056 at the beginning of the treatment on τ_1 = 10 day with the initial interval between injections ΔT^{stab} = 20.1 days: **a** shows the trajectories of growth and death of tumor cells; **b** shows the dynamics of formation of antibodies $A_V(V_0, \tau_1)$ at the 1st and $A_N(V_0, \tau_1)$ at the 2nd stage of the immune response (solid curve denotes $A_V(t)$, dashed curve denotes $A_N(t)$)



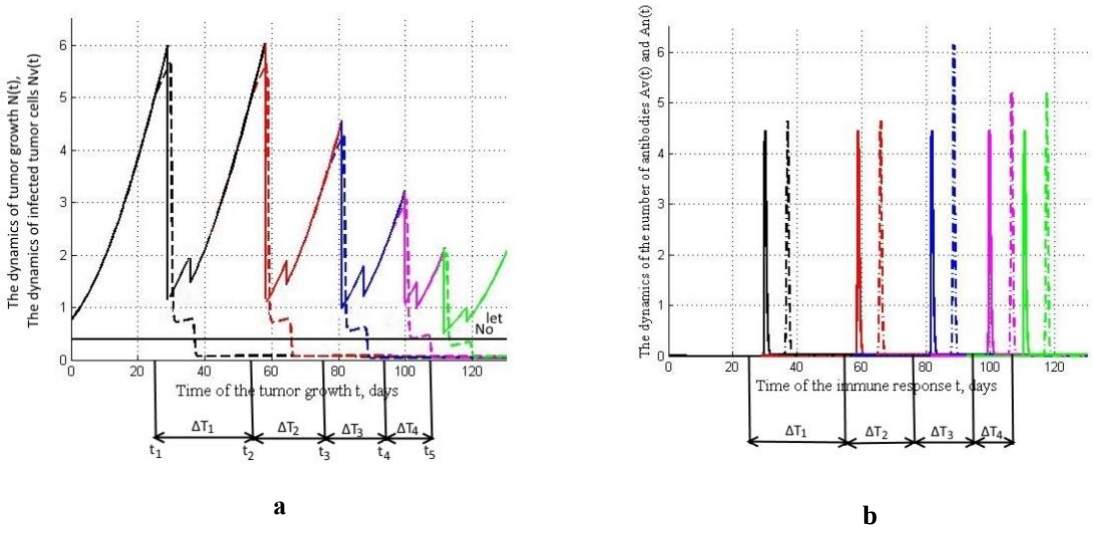
a **b**

Fig. 10. The strategy for multiple injection of the vaccine by reducing the interval between the doses V_0 = 0,06 at the beginning of the treatment on τ_1 = 20 day with the initial interval between injections ΔT^{stab} = 25.7 days: **a** shows the trajectories of growth and death of tumor cells; **b** shows the dynamics of formation of antibodies $A_V(V_0, \tau_1)$ at the 1st and $A_N(V_0, \tau_1)$ at the 2nd stage of the immune response (solid curve denotes $A_V(t)$, dashed curve denotes $A_N(t)$)

The dose of the viral vaccine was determined depending on the size of the tumor to implement the strategy of stabilizing the tumor size at the beginning of treatment $V_0^{stab}(\tau_1)$ (Fig.8 b). The interval between the first and second introduction of the vaccine ΔT_1^{stab} (τ_1) was also determined depending on the size of the tumor at the beginning of treatment based

on the condition of stabilization of the tumor size (Fig. 8,a). The moment of the second injection of the vaccine was defined as $\tau_2 = \tau_1 + \Delta T_1^{stab}$. Beginning from the third moment of the vaccine injection τ_3 and further τ_i, the moment of the subsequent injection of the vaccine was defined as $\tau_i = \tau_{i-1} + \Delta T_{i-1}$. The duration of the interval between injections was reduced by the step value and was calculated as $\Delta T_{i-1} = \Delta T_{i-2} - step$. In fact, the step value is the control parameter for the implementation of the strategy of gradual reduction of tumor size with each subsequent injections of a viral vaccine. The number of repeated injections of the vaccine to achieve regression of tumor growth depends on the step value. In the framework of the constructed model, this occurs when the number of tumor cells decreases below the lethality threshold (Fig. 9,a-10,a).

This strategy allows to achieve a reduction in the number of tumor cells below the lethality threshold only if the duration of tumor growth does not exceed 20 days (Fig. 10,a). For large tumors it is necessary to carry out surgery, or use a strategy to stabilize the growth of the tumor (Fig. 11,a).



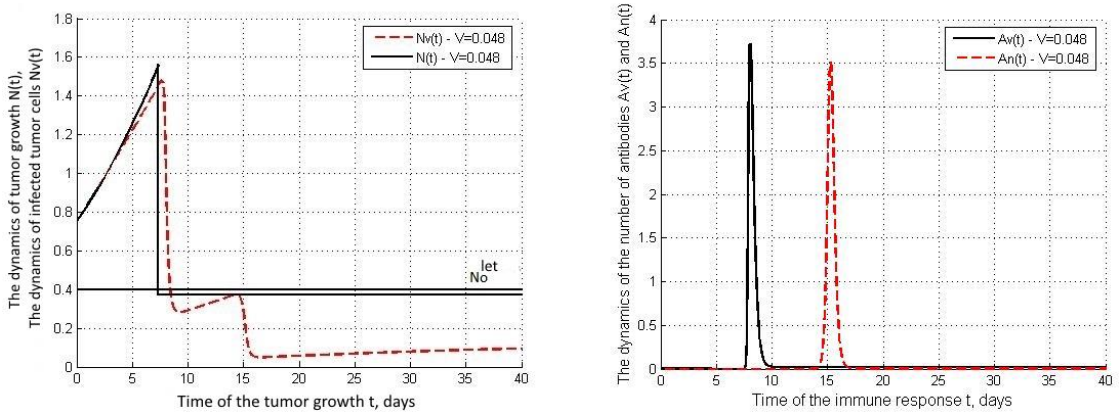
a **b**

Fig. 11. The strategy for multiple injection of the vaccine by reducing the interval between the doses $V_0 = 0{,}06$ at the beginning of the treatment on $\tau_1 = 25$ day with the initial interval between injections $\Delta T^{stab} = 28.9$ days: **a** shows the trajectories of growth and death of tumor cells; **b** shows the dynamics of formation of antibodies $A_V(V_0, \tau_1)$ at the 1st and $A_N(V_0, \tau_1)$ at the 2nd stage of the immune response (solid curve denotes $A_V(t)$, dashed curve denotes $A_N(t)$)

5.3. Strategy of single injection of the viral vaccines

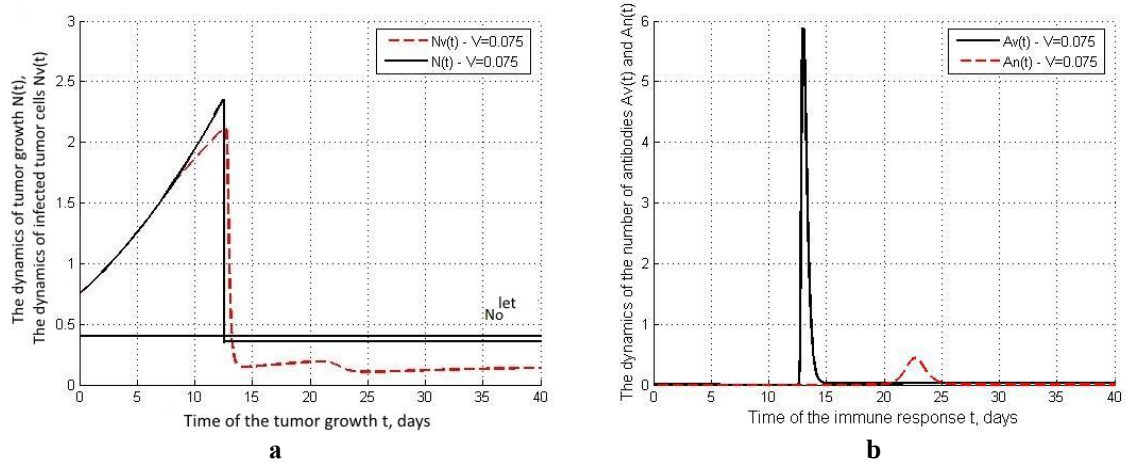
Testing the effectiveness of various doses of viral vaccine in a single injection at different points in tumor growth was carried out on the developed program module.

It was determined that even with a single injection of a viral vaccine in certain doses, it is possible to obtain a reduction in the number of tumor cells below the V0let threshold, i.e. achieve complete destruction (Fig.12a, 13a). At the same time, the number of antibodies produced at the first stage of the immune response exceeds their number at the second stage (Fig. 12b, 13b).



a **b**

Fig. 12. The strategy of a single lethal dose injection on $V_0^{let} = 0.048$ on $\tau_1 = 3$ day; **a** shows the trajectories of growth and death of tumor cells; **b** shows the dynamics of formation of antibodies $A_V(V_0, \tau_1)$ at the 1st and $A_N(V_0, \tau_1)$ at the 2nd stage of the immune response [19, p. 48, Fig. 9]



a **b**

Fig. 13. The strategy of a single lethal dose injection on $V_0^{let} = 0.075$ on $\tau_1 = 8$ day; **a** shows the trajectories of growth and death of tumor cells; **b** shows the dynamics of formation of antibodies $A_V(V_0, \tau_1)$ at the 1st and $A_N(V_0, \tau_1)$ at the 2nd stage of the immune response

Thus, the death of tumor cells with a single injection of lethal doses occurs immediately in the first stage of the immune response as a result of the formation of large amounts of antibodies against the virus $A_V(V_0)$ and a slight formation of antibodies against infected tumor cells $A_N(V_0)$.

As a result of the analysis of the obtained results, a dependence was constructed, indicating that the magnitude of lethal doses leading to the destruction of all tumor cells at the first stage of the immune response depends on the size of the tumor at the time of its introduction (Fig. 14). However, to achieve the complete destruction of tumor cells is possible only for small tumors, the growth of which does not exceed 8 days.

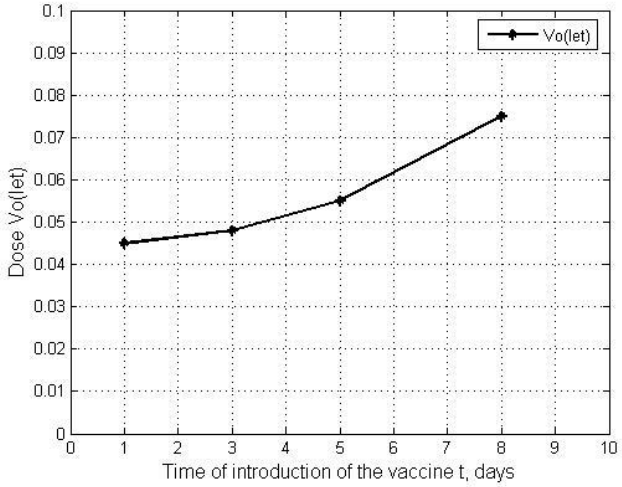


Fig. 14. The graph of lethal doses from the beginning of treatment $V_0^{\text{let}}(\tau_1)$ with a single injection of a viral vaccine [19, p. 49, Fig.11]

6. PREDICTING THE DURATION OF THE PERIODS BETWEEN THE REPEATED INJECTIONS OF VIRUS VACCINE FOR THE CLINIC

To predict the duration of the periods between repeated injections of the viral vaccine for the clinic according to the results obtained in the experiment on mice, it is proposed to use the well-known in biodynamics allometric ratio, which connects the rate of metabolic processes in the body with the body weight in mammals [24-26]:

$$m = a \cdot S^b, \tag{25}$$

where m is the body weight of the mammal, S is the rate of metabolic processes in mammals, a and b are constant parameters.

Allometric relations connect the body weight of animals and humans with a variety of other biological parameters that reflect the temporal characteristics of the processes of vital activity of the organism, including the duration of its life [24-26].

Then the ratio (25) can connect the body weight of the animal with any other time parameter. In this case, such a time parameter is considered the duration of the periods between successive injections of the viral vaccine in the implementation of the strategy of stabilizing the tumor size ΔT :

$$m = a \cdot (\Delta T)^b. \tag{26}$$

For two species of mammals, which are human and experimental mouse, we can write the allometric ratio of the form:

$$m^{human} = a \cdot (\Delta T^{human})^b \quad \text{and} \quad m^{mouse} = a \cdot (\Delta T^{mouse})^b, \tag{27}$$

where ΔT^{human} and ΔT^{mouse} denote the duration of the periods between the injections of viral vaccines for human being and for mouse.

To define the duration of the period between injections for the human being we can use the ratio:

$$\frac{m^{human}}{m^{mouse}} = \left(\frac{\Delta T^{human}}{\Delta T^{mouse}}\right)^b$$

Based on the fact that the average body weight values are known for a human being and a mouse, and the interval between successive injections of the vaccine is determined, the

duration of the period between injections of the vaccine for a person can be calculated from the equation:

$$\Delta T^{human} = \Delta T^{mouse} (\frac{m^{human}}{m^{mouse}})^{1/b} \tag{28}$$

The value of the parameter *b* was calculated as the slope of the straight line formed by the logarithmation of the allometric ratio, which relates the average body weight of different mammals and humans with the average life expectancy T_{life} (Fig. 15) [10]:

$$\ln m = b \cdot \ln T_{life} + \ln a = b \cdot \ln T_{life} + c \tag{29}$$

As a result of the regression analysis, the calculated value of the parameter *b* was obtained as *b* = 2,4981, which characterizes the slope of the regression line.

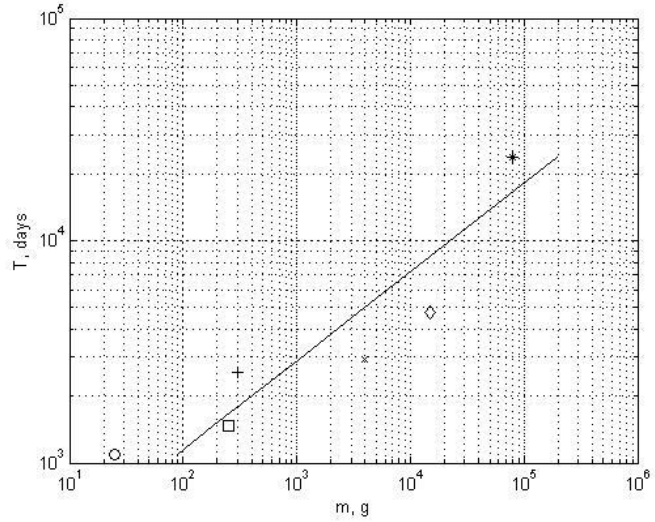


Fig. 15. Dependence of the life expectancy of animals on their body weight for ○ mouse, □ rats, + guinea pigs, x rabbits, ◊ dogs, and * humans [10]

Taking in equation (28) the mass of the mouse equal to m^{mouse} = 0,025 kg and the weight of a human being is equal to m^{human} = 70 kg, with *b* = 2,4981 = 2,5 and *1/b* = 0,39 we can calculate the time conversion factor from mouse to human.

$$K = (\frac{70}{0.025})^{0.4} = 23.9$$

Then the duration of the period between injections of the vaccine for a human being can be calculated from the expression:

$$\Delta T^{human} = \Delta T^{mouse} (\frac{m^{human}}{m^{mouse}})^{1/b} = \Delta T^{mouse} \cdot K \tag{30}$$

The results of the evaluation of the duration of the periods between repeated injections of viral vaccines in the implementation of the strategy of tumor size stabilization for humans and mouse are shown in the Table 1.

Table 1. Intervals between repeated injections of viral vaccines for humans and mouse obtained on the basis of allometric ratios

Dose of viral vaccine V_0 and when the vaccine was first	Interval between injections to stabilize tumor size in the experiment on mouse $\Delta T^{mouse}(V_0, \tau_1)$	Interval between injections to stabilize the size of the tumor in the clinic for humans $\Delta T^{human}(V_0, \tau_1)$

introduced τ_1		
$V_0 = 0.04$ on τ_1 =1 day	$\Delta T^{mouse}(V_0, \tau_1)$= 17.2 day	$\Delta T^{human}(V_0, \tau_1)$ =1,14 year
$V_0 = 0.047$ on τ_1 =3 days	$\Delta T^{mouse}(V_0, \tau_1)$= 18.4 day	$\Delta T^{human}(V_0, \tau_1)$ =1,22 year
$V_0 = 0.05$ on τ_1 =5 days	$\Delta T^{mouse}(V_0, \tau_1)$= 19.0 day	$\Delta T^{human}(V_0, \tau_1)$ =1,26 year
$V_0 = 0.056$ on τ_1 =10 days	$\Delta T^{mouse}(V_0, \tau_1)$= 20.1 day	$\Delta T^{human}(V_0, \tau_1)$ =1,33 year
$V_0 = 0.06$ on τ_1 =15 days	$\Delta T^{mouse}(V_0, \tau_1)$= 22.8 day	$\Delta T^{human}(V_0, \tau_1)$ =1,5 year
$V_0 = 0.06$ on τ_1 =20 days	$\Delta T^{mouse}(V_0, \tau_1)$= 25.7 day	$\Delta T^{human}(V_0, \tau_1)$ =1,7 year
$V_0 = 0.06$ on τ_1 =25 days	$\Delta T^{mouse}(V_0, \tau_1)$= 28.9 day	$\Delta T^{human}(V_0, \tau_1)$ =2 year

The method of allometric ratios is indirect and cannot guarantee 100% accuracy and reliability of the assessment of the duration of the periods between repeated injections of viral vaccines for their use in the clinic. However, this period of repeated injections of the viral vaccine may be a recommendation for the patient and for the doctor about the timing of the control examination. According to the results of the examination, it is necessary to decide on the condition of stabilization of the tumor size, which should not exceed the size of the tumor at the time of treatment. The results of the medical inspection should clarify the dose and adjust the strategy of repeated injections of the viral vaccine.

7. CONCLUSION

The results of the computational experiment conducted within this study indicate that the choice of cancer treatment strategy depends on the tumor size at the start of the treatment. The model also indicates that it is possible to reduce the number of tumor cells beyond the lethality threshold which guarantees that the tumor does not resume its growth.

For the small tumors (less than 8 days' growth as per our model), elimination of tumor cells can be achieved through single-shot virus-based vaccine administration. In this case, the death of tumor cells is caused by their destruction by the virus. However, in these conditions the number of antibodies produced against tumor cells is limited, which can result in recurrence of the tumor growth in future.

For bigger tumors (within 20 days' growth as per our model) elimination of tumor cells is possible if the vaccine is administered repeatedly with stepwise reduction of time periods between administrations.

The model developed within this study also makes it possible to define treatment strategy that may restrain the tumor development, i.e. lead to cancer chronification. Dosages and time intervals between vaccine administrations for this stabilization strategy were defined in the present study.

An advantage of this strategy is that it can be used for the tumors of any size. Thus it can be beneficial for the patients who cannot be subjected to surgical treatment, and creates new treatment possibilities for far-advanced cancer.

This study also proposes a method of transferring the results of the computational experiment to the treatment of humans, based on allometric relationships between human and animal body weights, enabling clinicians to calculate the appropriate intervals between repeated vaccine administrations. This method makes it possible to plan the return visit to the therapist to make a decision on subsequent vaccine administration.

Finally, results of the computational experiment based on mathematical modelling may substantially and meaningfully complement in vivo experiments for defining efficient cancer treatment strategies. Development of advanced methods of cancer treatment is highly dependent on the costs of conducting experiments. Active implementation of mathematical modelling approach on different stages of experimental research and clinical studies may contribute to the reduction of these costs as well.

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Appendix 1. Values of model parameters

Equation	Parameter	Description
$\frac{dN(t)}{dt}$ – (1-2)	$\alpha_N = 3.3613$, $\beta_N = 0.0332$ $N_\infty = 23$ $N_0 = 0.75$	The parameters of the function of Gompertz approximating the experimental curves of growth of population of tumor cells without vaccination (control)
$\frac{dN(t)}{dt}$ – (3)	$\tau_1 = 1$ $t_V = \tau_1 + Z_{CV}$ $Z_{CV} = 4.5$	The moment of the first injection of a viral vaccine The moment the beginning of the immune response against the virus Delay time of the immune response against the virus
$\frac{dN_V(t)}{dt}$ – (4-5)	$t_N = \tau_1 + Z_{CN}$	The moment the beginning of the immune response against infected tumor cells
	$Z_{CN} = 10.5$	Delay time of immune response against infected tumor cells
	$K_V = 0.25$ $K_{AV} = 0.8$ $K_{AN} = 0.8$	The constant coefficients of the equation of dynamics of the number of cells after a single injection of the vaccine
$\frac{dV(t)}{dt}$ – (6)	$\alpha_V = 0.1$	The reproductive rate of the virus
	$\beta_V = 15$	The rate of death of viruses in their interaction with antibodies
	$V_0 = 0.015$	The initial condition of equation (2), which reflects the dose of the viral vaccine
$\frac{dA_V(t)}{dt}$ – (7)	$\alpha_A = 100$	The rate of formation of antibodies from the single plasma cells
	$\beta_{AV} = 70$	The rate of loss of antibody due to the interaction with viruses
	$\beta_V = 5$	The rate of reduction of the number of antibodies due to natural destruction
	$A_V^{\max} = 1.05$	The maximum calculated number of the antibodies
$\frac{dC_V(t)}{dt}$ – (8)	$\alpha_C = 100$	The rate of formation of plasma cells
	$\beta_{CV} = 4.5$	The size factor
	$C_{VN} = 0.001$	The initial number of plasma cells
$\frac{dA_N(t)}{dt}$ – (9)	$\alpha_{AN} = 30$	The rate of formation of antibodies from the single plasma cells
	$\beta_{AN} = 6.2$	The rate of decline of antibodies due to the interaction with the tumor cells
	$\beta_{NN} = 6.3$	The rate of the reduction of the number of antibodies due to the natural destruction
	$A_N^{\max} = 4.64$	The maximum calculated number of antibodies
$\frac{dC_N(t)}{dt}$ – (10)	$\alpha_{CN} = 76.677$	The rate of formation of plasma cells
	$\beta_{CN} = 38$	The size factor
	$C_{NN} = 0.0001$	The initial number of plasma cells
$P(t)$ – (11)	$\alpha_p = 0.3$ $K_p = 0.95$ $\beta_p = 1/t^*$	The parameters of the p(t) function describing the dynamics of the decrease in the proportion of rapidly proliferating cells as the tumor size increases The moment at which the number of fractions of rapidly and

	t^* = 35 суток	slowly proliferating cells are equal
$\frac{dN(t)}{dt}$ – (13)	ε_V = 4.5 сут.	The delay in the growth of tumor cells as a result of their death under the action of the virus
	ε_V = 9.8 сут.	The delay in the growth of tumor cells as a result of their death under the action of antibodies against infected tumor cells
	t_1^V = 5.82 t_1^N = 12.32	The moments of reaching the maximum number of infected tumor cells by the beginning of the immune response
	t_2^V = 7.13 t_2^N = 14.29	The moments of reaching the minimum number of infected tumor cells by the end of the immune response
	$N_V^V\left(t_1^V\right)$ = 1.31, $N_V^N\left(t_1^N\right)$ = 1.15	The maximum values of the number of infected tumor cells before the immune response at each of the two stages of their death
	$N_V^V\left(t_2^V\right)$ = 0.84, $N_V^N\left(t_2^N\right)$ = 0.1	The minimum values of the number of infected tumor cells at the end of the immune response at each of the two stages of their death
	$\Delta N_V^V\left(t_1^V\right)$ = 0.47, $\Delta N_V^N\left(t_1^N\right)$ = 1.04	The number of infected cells killed in the first and second stages of immune system stimulation

