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OPTIMAL CONTROL

Numerical Methods of Optimal Control of the HIV-Infection Dynamics

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Abstract—The problem of optimal control of a dynamic model of HIV-infection development in humans is solved. This work illustrates the possibilities of applying numerical methods for optimization of the treatment process.

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INTRODUCTION

The results of simulation of the dynamics of the development of HIV-infection, caused by the human immunodeficiency virus, for two limiting regimes are presented. Reflecting the real development of the disease, this information shows that the terminal state of the immune system (the irreversible manifestation of the acquired immunodeficiency syndrome (AIDS)) comes on the 2865th day without treatment, and, in the case of the maximal intensive treatment with two active medications during the entire period of the disease, it comes on the 2931th day. In other words, a ten-year treatment results in an increase in the lifetime of the patient by two months.

Obviously, this result, characterizing the severe character of the HIV-infection in its fullest extent, deprives mathematical control methods of any applied prospective for the problems of HIV-infection treatment; since it is not permitted to increase the quantity of medications harmful for the patients' health, medication control in the second regime is still located on the boundary of the feasible domain. Therefore, the mathematical models of HIV-infection are considered by the authors as a typical object for simulation experiments in the theory of the control of catastrophes, which endeavors to minimize their inevitable damage. In this catastrophe, the damage is the patient's death, and the optimizing control should attempt to postpone its time.

The results of these experiments are presented in Section 5, where the treatment programs, obtained by the numerical method based on the necessary optimality conditions, which are not the best, are shown. They allow us to prolong the lifetime of the patient treated by the same medications up to 8530 days. In this case, the total medication intake decreased approximately by a factor of 15, compared with the continuous treatment regime.

The mathematical optimal control technologies of obtaining this result are presented in this paper. We put in the forefront their basic characteristics.

Before the 1950s, control science consisted of the regulation theory generalized simple technique of using feedback and feedforward links. Then, the design of optimal regulators and the problem of tracking the optimal trajectories of a spacecraft led to the development of optimal control theory, for which the Pontryagin maximum principle [1] and the Bellman dynamic programming method [2], together with computational methods based on both of them, became the basic tools. The methods of regulation by the correction of the current state of the object were replaced by functional methods, utilizing the principle of control of the future from the present. One of these methods [3–6], probed on solving complex technical problems, is laid as the foundation of the computational algorithm used in the paper.

Control theory has become a very common *technological* tool in engineering sciences, and, in this paper, it is also applied in this quality. The existence of such a tool explains quite well the *possibility* of solution of the problem considered in this paper. Here, however, it is important to answer the question why the computed trajectory *qualitatively* outperforms the solution, which is *apparently* the best at the point of common sense. One may attempt to find the answer in the philosophical aspects of optimal control theory that is useful both for its further development and practice as well.

Control theory is the result of human intellectual activity; however, it has taken the position of a separate subject. We explain this fact by examples. From the point of view of a civil airplane pilot, by switching the autopilot on in the cruising mode, the control system makes his physical and intellectual work easier. From the point of view of a military airplane pilot, who uses the computer intellectual system of operation maintenance [7], or a cosmonaut, who sets up the vehicle tra-

jectory-tracking problem to the vehicle computer [5], these prompting, advising, and commanding control systems amplify their intellectual abilities; moreover, they are regarded as partners. Unlike other artificial intelligence systems, which model the activity of the living brain, these systems do an intellectual job that is impossible for a human. In fact, the solution of the trajectory-tracking problem without control theory requires the ability to predict the future and to choose the best variant out of an uncountable number of variants of this future, which, of cause, neither groups of astronomers nor groups of cosmonauts can do. Hence, one may well say that control theory has a *superintelligence* [8].

In this paper, we consider a trajectory-tracking problem, which is analogous by setup, by volume, and by complexity, but which now is the trajectory-tracking problem of a disease, which also cannot be solved without control theory, just like in cosmonautics. The solution (presented in Section 5), which regulates the hourly medication intake over more than two decades, cannot be formulated by physicians' consultations. It is also impossible to guess the optimal 20-year regime between two limiting 10-year regimes. The mathematical algorithm, though, allows a patient to be in the condition of clinical death (anabiosis, if we wish to speak the language of deep space exploration) in the course of intermediate computational iterations, in order to return his or her trajectory into the domain of life after one hundred or one thousand subsequent iterations. In observing how a computer prolongs the life of a doomed person by a minute, by an hour, by a day, by a year, or by a decade, just manipulating complex formulas, iteration after iteration, it impossible to reject the right of this "advocate of life" to be called reasonable.

The explanation for why a computed solution outperforms the intuitively best solution is the fact that the superintelligence of mathematics outperforms natural human intelligence in solving complex control problems. Therefore, in medicine, where these problems appear, the methods of control theory are inevitable; without them, it is impossible to cope with such formidable challenges to human health as HIV. The understanding of this situation should reduce the time needed to put these mathematical instruments into practice, instruments that exact sciences spent great efforts and centuries to create.

It is likely that the principles of control theory, predicting the future, and controlling it from the present do not constitute a new patent for biology as the examples of animal behavior before the approach of a nature catastrophe show; however, it is worth it to learn to use them purposefully.

This paper pursues the following methodical objectives: it does not pretend to solve the problem, but it intends to demonstrate the opportunity that mathematical methods of control offer. Therefore, the medical and biological justifications of the simulation models of the HIV-infection dynamics are accepted without discussion. The methods considered still remain applicable for improved and extended models.

In the applied aspect, first of all, the instruments proposed can be invoked for systems that calculate the individual treatment programs that may be adjusted and modified easily to changes in the progression of the illness and in response to the creation of new medications. Another area of application is the systems of express approval of new medications developed. A computer is able to give a preliminary conclusion on their efficacy, the details of their action on the organism, and directions for usage, which currently takes years in practice.

1. THE MODEL OF THE DYNAMICS OF HIV-INFECTION

1.1. Immune System Study

The problems of using mathematical simulation and control methods in biology and medicine were formulated by Norbert Wiener, the patriarch of cybernetics [9]. The mathematical models of the human immune system were constructed and studied in a number of publications of Russian and foreign authors [10–15]. In [14, 15], the mathematical models of immune system interaction with HIV are studied. Some problems of optimization of immune processes including HIV-infection were considered in [16–21].

In this paper, we set up and solve the problem of optimal control of HIV-infection treatment based on the mathematical model of [15]. The numerical optimization method we use allows us to solve it in an exact formulation, without using any artificial assumptions and simplifications, which are unavoidable in analytical study and solution of problems of this complexity. It is worth noting that in the statement of problems of designing optimal programs for treating HIV-infection, we lean on papers by V.V. Pokrovskii and his colleagues [22].

1.2. The Controlled Model of HIV-Infection

The modified control model constructed based on the uncontrolled model of [15] is described by the system of ordinary differential equations

$$\frac{dT(t)}{dt} = S_1 - \frac{S_2 V(t)}{B_S + V(t)} - \mu_T T(t)$$

$$+ \frac{\lambda_1}{C + V(t)} T(t)V(t) - (\eta_1(t) k_S V_S(t) + k_r V_r(t))T(t),$$

$$\frac{dT_S(t)}{dt} = \eta_1(t) k_S V_S(t) - \mu_{Ti} T_S(t)$$

$$- \frac{\lambda_2}{C_i + V(t)} T_S(t)V(t),$$

$$\frac{dT_r(t)}{dt} = k_r V_r(t)T(t) - \mu_{Ti}T_r(t) - \frac{\lambda_2}{C_i + V(t)}T_r(t)V(t),$$

$$\frac{dV_S(t)}{dt} = (1-q)\frac{\lambda_3}{C_i + V(t)}T_S(t)V(t) - k_V T(t)V_S(t) + \eta_2(t)\frac{G_S V_S}{B + V(t)}, \quad (1.1)$$

$$\frac{dV_r(t)}{dt} = \frac{\lambda_3}{C_i + V(t)}T_r(t)V(t) + q\frac{\lambda_3}{C_i + V(t)}T_S(t)V(t) - k_V T(t)V_r(t) + G_r(V(t))\frac{V_r(t)}{B + V(t)},$$

$$\frac{d\eta_1(t)}{dt} = c_1(1 - \eta_1(t) - u_1),$$

$$\frac{d\eta_2(t)}{dt} = \frac{c_2}{1 - c_3}(1 - \eta_2(t) - u_2(c_3 - 1)).$$

Here, the first five equations of system (1.1) repeat the equations of the model of [15] and the last two are introduced by us, in order to convert the model to a form that allows us to set up the control problem in terms of the theory of optimal processes [1] and numerical optimization methods [3, 4].

The phase variables in the model of [15] are T, T_S, T_r, V_S, and V_r. The treatment functions $\eta_1$and η_2 in the model of [15] are defined as functions of time and describe the action of medications on the system. In this paper, the process of medication intake is not continuous, because it assumes intervals of prescribing and canceling. In order to describe the dynamics of the treatment functions η_1 and η_2 in the course of the process of prescribing and canceling the treatment in controlled model (1.1), the sixth and the seventh differential equations are introduced.

Thus, system (1.1) includes seven phase variables T, T_S, T_r, V_S, V_r, η_1, and η_2. Their meaning and the basic mechanism of their interaction are described below.

T is the concentration of noninfected CD4 + T cells (below T-cells). These cells play the crucial role in human immune system functioning. Namely, they react to foreign matter (including viruses) ingress and generate an immune response. In a normal situation, the concentration of these cells in the blood is about 1000 units per a cu. mm. During a virus attack, T-cells start to multiply intensively, reinforcing the immune system (this effect is taken into account in the fourth term of the first equation, which shows the increase of the concentration of T-cells when the virus presents). Thus, the T-cell level serves as a basic indicator of the immune system working capacity.

The phase variables T_S and T_r describe the population of infected T-cells:

T_S is the concentration of T-cells infected by the immunodeficiency virus V_S sensitive to the action of medications,

T_r is the concentration of T-cells infected by the immunedeficiency virus V_r resistant to chemotherapy.

The immunodeficiency virus specific feature is its mutation ability. Being treated by chemotherapy, the virus elaborates defensive mechanisms counteracting the action of medications. This effect is called *resistance*, and the virus resulting from mutation is called *resistant.* The population of the immunodeficiency virus V considered in the model is subdivided into two classes:

V_S is the concentration of HIV sensitive to the action of medications,

V_r is the concentration of HIV resistant to chemotherapy.

$V(t) = V_S(t) + V_r(t)$ is the generic population of the virus at the time t.

As all viruses, HIV is not capable of reproducing itself without a "host." HIV inserts copies of its DNA into the DNA of host cells. When a host cell divides, it makes copies of the virus. In invading the organism, HIV aims toward T-cells first. It deprives them of their immune function and impels them to make copies of the virus.

The fact that T-cells play a crucial role in the immune response is precisely the basic reason for the destructive action of HIV; the presence of the immunodeficiency virus population in the organism results in the T-cell concentration decreasing, and hence, to immunity weakening. In the background of weaken immunity, secondary infections develop in the human organism, which results in a lethal outcome.

The infection of the T-cells and their change from the population T to the populations T_S and T_r is des-cribed by the last terms of the first equation and the first terms of the second and the third equations of model (1.1).

The destruction of infected T-cells T_S and T_r caused by virus containing is presented by the third terms of the second and the third equations of (1.1). At the same time, the infected T-cells throw new copies of the virus into the system, which is taken into account by the positive first terms of the fourth and the fifth equations of the model.

We assume that T-cells infected by the resistant virus throw the copies of the resistant virus into the system (which is reflected in the third term of the third equation of (1.1)). However, T-cells infected by the sensitive virus can produce copies of both sensitive and resistant viruses (the third term of the second equation, the first term of the fourth equation and the second term

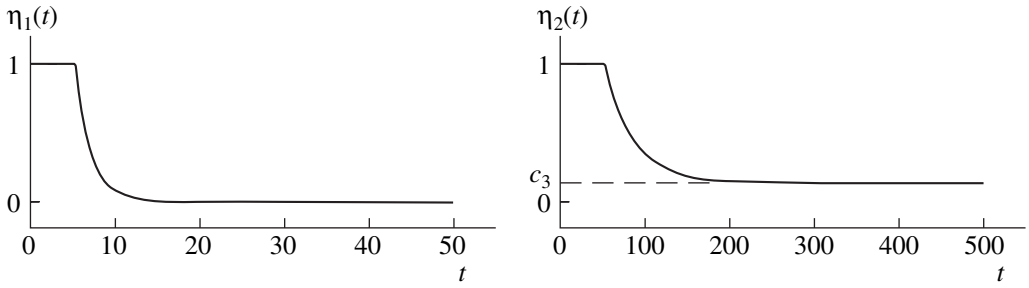

Fig. 1. Treatment functions in an uncontrolled model.

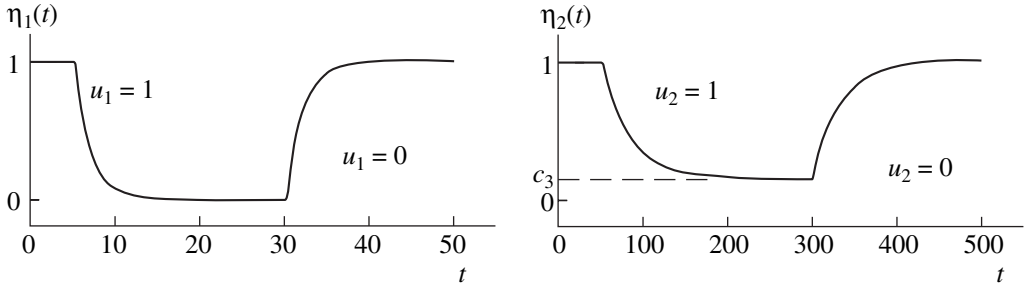

Fig. 2. Treatment functions in a controlled model.

of the fifth equation of (1.1)). The mutation capability of the virus is determined by the parameter q.

It is assumed that the resistant virus starts to come into the system from an external source (the last term of the fifth equation) only after the entire virus population achieves a certain threshold concentration. Biologically, it means that when the virus concentration in the blood is large enough, the information on protection from medications is transmitted to the lymphoid system, where the sensitive virus also begins to be replaced by the resistant one. In system (1.1), this effect is described by a discontinuous function G_{n}

$$G_r(V) = \begin{cases} 0 \text{ for } V < V_0, \\ G_S \text{ for } V \geq V_0. \end{cases} \tag{1.2}$$

In the uncontrolled model of [15] (the first five equations of (1.1)), the treatment functions $\eta_1(t)$ and $\eta_2(t)$, which take the action of two medications on the system into account, are determined by the following functions of time

$$\begin{aligned} \eta_1(t) &= \exp(-c_1(t-t_0)), \\ \eta_2(t) &= \max\{\exp(-c_2(t-t_0)), c_3\}. \end{aligned} \tag{1.3}$$

Their graphs are presented in Fig. 1. The first function describes decreasing of the last term of the first equation, reflecting the effect of T-cell infecting by the sensitive virus, the second one describes the effect of suppressing the virus inflow into the blood from the lymphoid system. The resistant group of the virus is not affected by the treatment.

A more detailed description of the uncontrolled model is presented in [15].

The model in [15] does not describe any treatment pauses. At the same time, exponential functions (1.3) point out the dynamic character of the medication interaction process, which may be described by differential equations. This is done in the sixth and the seventh equations of (1.1). Here, the controlling variables u_1 and u_2 (the treatment switches) are introduced, which may take values of 0 and 1. In the case of $u_1 = 1$ and $u_2 = 1$, the medications are prescribed to a patient, and, in the case of $u_1 = 0$, $u_2 = 0$, they are cancelled. The graphs of the solutions of the sixth and the seventh equations of (1.1) are given in Fig. 2.

The comparison of Fig. 1 and Fig. 2 demonstrates the same behavior of both treatment functions in model (1.3) and (1.1), in the case if the treatment is "switched on." In (1.1), the parameters of the dynamics of their change for the case of switched-on treatment are retained for the case of switched-off treatment.

The values of constants of the model of [15] used for integrating system (1.1) are given in Table 1.

2. NUMERICAL SIMULATION OF UNCONTROLLED HIV-INFECTION DYNAMICS

Consider the results of simulation of the dynamics of HIV-infection development in two limiting regiments: without treatment and with continuous treatment during the entire period of illness.

Table 1. Constants and parameters list

Symbol	Description	Value
μ_T	Noninfected *CD*4cell dying	0.005/day
μ_{Ti}	Infected cell *CD*4 dying	0.25/day
k_S	*T*-cell affection by the sensitive virus	0.0005 cu. mm/day
k_r	*T*-cell affection by the resistant virus	0.0005 cu. mm/day
k_V	Virus loss, caused by immune response	0.0062 cu. mm/day
λ_1	Noninfected *CD*4cell reproduction rate	0.025/day
λ_2	Infected *CD*4cell reproduction	0.25/day
λ_3	Virus reproduction rate in the blood	0.8/day
G_s	The parameter of the external lymphoid source of the sensitive virus	41.2 cu. mm/day
G_r	The parameter of the external lymphoid source of the resistant virus	41.2 cu. mm/day
V_0	Resistance threshold	0.5/cu. mm
q	Resistance virus fraction, obtained as the result of normal virus reproduction	10^{-7}
C	Noninfected *CD*4cell saturation coefficient	47.0/cu. mm
C_i	Infected *CD*4cell saturation coefficient	47.0/cu. mm
B	External virus source saturation coefficient	2.0/cu. mm
B_s	*CD*4cell source saturation coefficient	13.8/cu. mm
S_1	*CD*4cell inflow without virus	4.0 cu. mm/day
S_2	*CD*4cell inflow decrease	2.8 cu. mm/day
c_1	Treatment parameter: *CD*4cell affection rate suppressing	0.5
c_2	Treatment parameter: virus inflow from an external lymphoid source rate suppressing	0.025
c_3	Treatment parameter: maximum possible suppressing of the virus inflow from an external lymphoid source	0.15

2.1. The Dynamics of HIV-Infection without Treatment

In Fig. 3, the results of numerical integration of equations (1.1) without treatment are presented. In the model of [15], this regiment corresponds to the values of $\eta_1(t) \equiv 1$ and $\eta_2(t) \equiv 1$, and, in model (1.1), it corresponds to the constant values of switches $u_1(t) \equiv 0$ and $u_2(t) \equiv 0$.

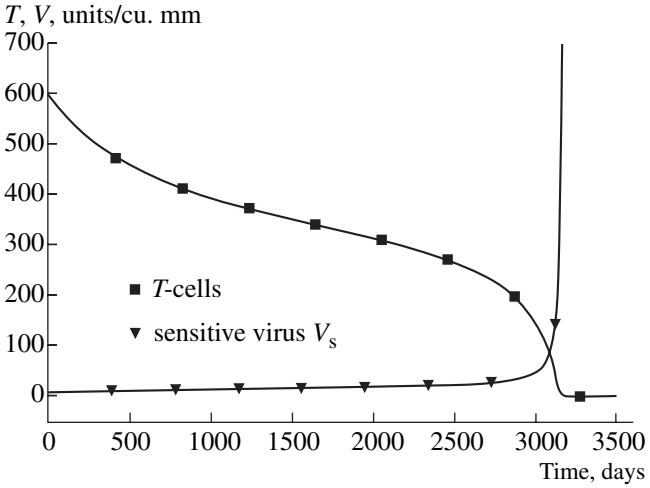

Fig. 3. HIV-infection dynamics without treatment. Initial conditions: $T(0) = 600$ units/cu. mm, $T_S(0) = 0$ units/cu. mm, $T_r(0) = 0$ units/cu. mm, $V_S(0) = 10$ units/cu. mm, $V_r(0) = 0$ units/cu. mm, $\eta_1(t) \equiv 1$, $\eta_2(t) \equiv 1$.

The computations carried out for (1.1) with the same initial values demonstrated the precise coincidence with the computations of [15]. This fact serves as the correctness criterion of our computational work with the model.

The graphs of Fig. 3 agree with the results of clinical investigations [14, 15]. During the first several weeks after the period of acute infection, the amount of *T*-cells falls gradually from 600–800 units per a cu. mm to zero for a time period of 9–10 years (the amount of *T*-cells of a healthy person ranges between 800 and 1200 units per a cu. mm).

2.2. The Dynamics of HIV-Infection in the Case of Continuous Treatment

In this case, the mutation mechanism of the virus starts acting. As a result, two stages in the dynamics of the process are distinguished: fast mutation and the following relatively slow development of the disease.

In the uncontrolled model of [15], the continuous treatment regime is described by the treatment functions (1.3) presented in Fig. 1. In (1.1), this regime corresponds to the constant values of switches $u_1(t) \equiv 1$, $u_2(t) \equiv 1$.

The short interval. The virus mutation process under the action of medications is characterized by rapid dynamics; the sensitive virus is replaced by its resistant form within several weeks. This process is explored qualitatively in [15] and corresponds to the data of clinical observations. The dynamics of the process are illustrated in Fig. 4, in which the results of the numerical integration of equations (1.1) with the same initial conditions as in Fig. 3 are shown. This allows us to compare the development of the disease treated by means of chemotherapy and without treatment.

Long interval. The results of integration of (1.1) in the case of continuous treatment for a long period of time are presented in Fig. 5. The comparison of Fig. 5 and Fig. 3 shows that they actually differ by a short interval of rapid dynamics (Fig. 4), after which the treatment stops acting on the modified resistant virus. As a result, the continuous use of chemotherapy for almost 10 years postpones the last stage of the HIV-infection, causing a lethal outcome (which is called AIDS and is characterized conditionally by passing the threshold of 200 units per a cu. mm in the concentration of *T*-cells) in just 66 days.

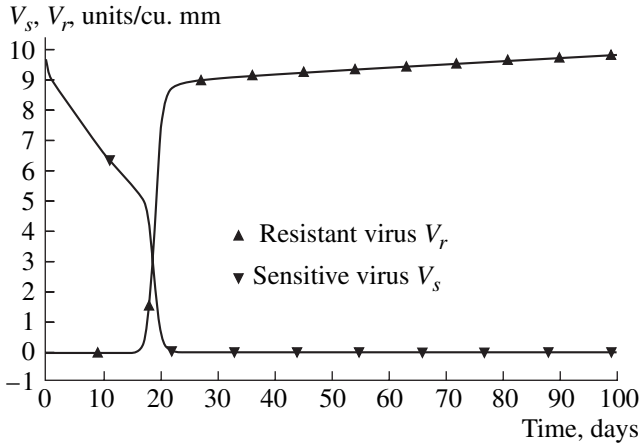

Fig. 4. HIV-infection dynamics in the case of continuous treatment for 100 days. Initial conditions are the same as for the regime in Fig. 3.

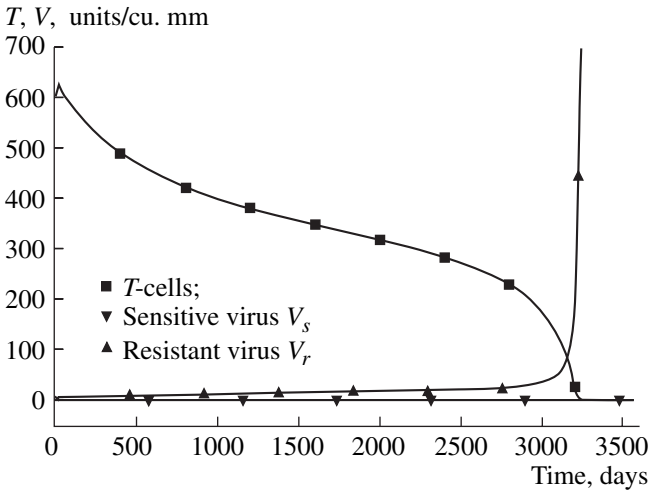

Fig. 5. HIV-infection dynamics in the case of continuous treatment over 3500 days. Initial conditions are the same as for the regime in Fig. 3.

3. STATEMENT OF THE PROBLEM OF OPTIMAL CONTROL OF THE TREAMENT PROCESS

The results of modeling of limiting regiments with and without application of chemotherapy point out the extremely high resistance of the virus to the action of medications. The qualitative analysis of complicated nonlinear model (1.1) does not give the opportunity to point out the direction of modification of the continuous treatment program at least, since the control is already located on the boundary of the feasible domain, and it seems obvious that any decrease of the amount of medications cannot improve the patient's conditions. The existence of treatment programs, better than the continuous treatment, is problematic, and this question can be investigated by means of numerical experiments with only the model.

The objective of therapy is the prolongation of the patient's lifetime. In order to set up a mathematical problem, one has to find the quantitative characteristics of health conditions that allow us to formulate this objective quantitatively. In the case of HIV-infection, this quantitative characteristic is the *T*-cell concentration in the blood. In [16], three severity categories of the illness are distinguished, according to the concentration level in units per cu. mm: (1) more than 500, (2) from 200 to 500, and (3) less than 200.

The patients of the third category develop AIDS, ending up with a lethal outcome. The lowest value of *T*-cell concentration is the natural bound of the immune system process studied. In the mathematical model, this means that, in a seven-dimensional phase space (1.1), one should consider its trajectories, ending on the hypersurface

$$T(t) - T^* = 0, \quad T^* = 200 \text{ units per cu. mm.} \qquad (3.1)$$

The problem of prolongation of the patient's lifetime is to provide that the immune system would achieve bound (3.1) as late as possible. In a formal setup, the objective functional J in the treatment optimization problem should be the termination time

$$J[u_1(t), u_2(t)] = t_\kappa = \{t \mid T(t) = T^*\}, \qquad (3.2)$$

when the trajectory of system (1.1) reaches hypersurface (3.1) for the first time.

Formula (3.2) points out that the value of the functional T_κ is determined by the choice of controlling functions $u_1(t)$ and $u_2(t)$. Thus, the numerical algorithm should be committed to find the functions for which functional (3.2) attains its maximum value among all functions, bounded by the conditions $u_1(t) \in \{0, 1\}$ and

$u_2(t) \in \{0, 1\}\ \forall t \in [t_н, t_к]$, where t_i is the initial time instant,

$$J[u_1(t), u_2(t)] = t_к = \{t \mid T(t) = T^*\} \longrightarrow \max_{u_1(t), u_2(t)}. \quad (3.3)$$

4. THE QUANTUM LOCALLY OPTIMAL ALGORITHM OF SUCCESIVE APPROXIMATIONS

4.1. The Basic Equations of the Optimization Method of [3, 4]

We introduce the seven-dimensional vector of phase variables, conjugate to the phase coordinates of system (1.1)

$$p(t) = \{p_T, p_{TS}, p_{Tr}, p_{VS}, p_{Vr}, p_{\eta 1}, p_{\eta 2}\} \quad (4.1)$$

and form the Hamilton–Pontryagin function [1]

$$\begin{aligned} H(T, T_S, T_r, V_S, V_r, \eta_1, \eta_2, p_T, p_{TS}, p_{Tr}, p_{VS}, p_{Vr}, \\ p_{\eta 1}, p_{\eta 2}, u_1, u_2, t) = p_T\Big[S_1 - \frac{S_2 V(t)}{B_S + V(t)} - \mu_T T(t) \\ + \frac{\lambda_1}{C + V(t)} T(t) V(t) - (\eta_1(t) k_S V_S(t) + k_r V_r(t) T(t))\Big] \\ + p_{TS}\Big[\eta_1(t) k_S V_S(t) T(t) - \mu_{Ti} T_S(t) \\ - \frac{\lambda_2}{C_i + V(t)} T_S(t) V(t)\Big] \\ + p_{Tr}\Big[k_r V_r(t) T(t) - \mu_{Ti} T_r(t) - \frac{\lambda_2}{C_i + V(t)} T_r(t) V(t)\Big] \\ + p_{VS}\Big[(1 - q)\frac{\lambda_3}{C_i + V(t)} T_S(t) V(t) \\ - k_V T(t) V_S(t) + \eta_2(t)\frac{G_S V_S(t)}{B + V(t)}\Big] \\ + p_{Vr}\Big[\frac{\lambda_3}{C_i + V(t)} T_r(t) V(t) + q\frac{\lambda_3}{C_i + V(t)} T_S(t) V(t) \\ - k_V T(t) V_r(t) + G_r(V(t))\frac{V_r(t)}{B + V(t)}\Big] \\ + p_{\eta 1}[c_1(1 - \eta_1(t) - u)] \\ + p_{\eta 2}\Big[\frac{c_2}{1 - c_3}(1 - \eta_2(t) + u_2(c_3 - 1))\Big]. \end{aligned} \quad (4.2)$$

Construct the system of differential equations for costate variables

$$\begin{aligned} \frac{dp_T}{dt} &= p_T\Big(\mu_T - \lambda_1\frac{V(t)}{C + V(t)} + \eta_1(t) k_S V_S(t) + k_r V_r(t)\Big) \\ &- p_{TS}\eta_1(t) k_S V_S(t) - p_{Tr} k_r V_r(t) \\ &+ p_{VS} k_V V_S(t) + p_{Vr} k_V V_r(t), \\ \frac{dp_{TS}}{dt} &= p_{TS}\Big(\mu_{Ti} + \lambda_2\frac{V(t)}{C_i + V(t)}\Big) \\ &- (p_{VS}(1 - q) + p_{Vr} q)\lambda_3\frac{V(t)}{C_i V(t)}, \\ \frac{dp_{Tr}}{dt} &= p_{Tr}\Big(\mu_{Ti} + \lambda_2\frac{V(t)}{C_i + V(t)}\Big) - p_{Vr}\lambda_3\frac{V(t)}{C_i + V(t)}, \\ \frac{dp_{VS}}{dt} &= p_T\Big(\frac{S_2 B_S}{(B_S + V(t))^2} - \lambda_1\frac{T(t) C}{(C + V(t))^2} \\ &+ \eta_1(t) k_S T(t)\Big) - p_{TS}\eta_1(t) k_S T(t) + p_{VS} k_V T(t) \\ &+ (p_{TS}\lambda_2 T_S + p_{Tr}\lambda_2 T_r - p_{VS}(1 - q)\lambda_3 T_S \\ &- p_{Vr} q\lambda_3 T_S - p_{Vr}\lambda_3 T_r)\frac{C_i}{(C_i + V(t))^2} \\ &+ \frac{p_{Vr} G_r V_r(t) - p_{VS}\eta_2(t) G_S(B + V_r(t))}{(B + V(t))^2}, \\ \frac{dp_{Vr}}{dt} &= p_T\Big(\frac{S_2 B_S}{(B_S + V(t))^2} - \lambda_1\frac{T(t) C}{(C + V(t))^2} + k_r T(t)\Big) \\ &- p_{Tr} k_r T(t) + p_{Vr} k_V T(t) + (p_{TS}\lambda_2 T_S + p_{Tr}\lambda_2 T_r \\ &- p_{VS}(1 - q)\lambda_3 T_S - p_{Vr} q\lambda_3 T_S - p_{Vr}\lambda_3 T_r)\frac{C_i}{(C_i + V(t))^2} \\ &+ \frac{p_{VS}\eta_2(t) G_S V_S(t) - p_{Vr} G_r(B + V_S(t))}{(B + V(t))^2}, \\ \frac{dp_{\eta 1}}{dt} &= (p_T - p_{TS}) k_S V_S(t) T(t) + p_{\eta 1} c_1, \\ \frac{dp_{\eta 2}}{dt} &= p_{\eta 2}\frac{c_2}{1 - c_3} - p_{VS}\frac{G_S V_S(t)}{B + V(t)}. \end{aligned} \quad (4.3)$$

The optimization method of [3, 4] allows us to solve maximization problem (3.3) by means of successive increase in the values of the functional J (3.2). The

algorithm changes the controlling functions $u_1(t)$ and $u_2(t)$ purposefully, by using the information obtained by solving systems (1.1) and (4.3) simultaneously. In this case, the following boundary conditions on the costate variables at the right end of the trajectory

$$\begin{aligned} p_T(t_{\text{st}}) &= -\left(\frac{dT}{dt}\Big|_{t=t_{\text{st}}}\right)^{-1}, \\ p_{TS}(t_{\text{st}}) &= p_{Tr}(t_{\text{st}}) = p_{VS}(t_{\text{st}}) = p_{Vr}(t_{\text{st}}) \\ &= p_{\eta 1}(t_{\text{st}}) = p_{\eta 2}(t_{\text{st}}) = 0 \end{aligned} \tag{4.4}$$

correspond to the problem of the maximization of functional (3.2) on hypersurface (3.1).

Because of the discontinuity of function $G_r(V)$ (1.2), the right-hand side of (1.1) changes abruptly, when it passes across the hypersurface

$$\Omega(V_S,V_r) = V_S + V_r - V_0 = 0. \tag{4.5}$$

Therefore, when the trajectories of system (1.1) pass hypersurface (4.5), the costate variable vector-valued function (4.1) satisfies the jump condition of [4]

$$\begin{aligned} p_{VS}(t-0) &= p_{VS}(t+0) - \nu\frac{\partial\Omega}{\partial V_S} = p_{VS}(t+0) - \nu, \\ p_{Vr}(t-0) &= p_{Vr}(t+0) - \nu\frac{\partial\Omega}{\partial V_r} = p_{Vr}(t+0) - \nu. \end{aligned} \tag{4.6}$$

The coefficients of the jump ν are determined by the expression

$$\nu = \frac{p_{Vr}(t+0)G_S\dfrac{V_r(t)}{B+V(t)}\operatorname{sgn}[V_S(t-0)+V_r(t-0)-V_0]}{\bar{f}_{VS}[(x(t),u(t),t])+\bar{f}_{Vr}[((x)(t),u(t),t])}. \tag{4.7}$$

Here, $\bar{f}_{VS}$ 1 and $\bar{f}_{Vr}$ are the right-hand sides of the fourth and fifth equations of hypersurface (4.5).

4.2. The Formula for the Increment of the Functional [3, 4]

The process of successive improvement of the control is performed by using the formula for the increment of the functional, which is constructed in the following way for this specific problem.

For given control functions $u_1 = u_1(t)$ and $u_2 = u_2(t)$, we solve the Cauchy problem for system (1.1) with given initial conditions (initial conditions from Fig. 3). Thus, its trajectory

$$\begin{aligned} x(t) = \{&T(t), T_S(t), T_r(t), V_S(t), V_r(t), \eta_1(t), \eta_2(t)\}, \\ &t_{\text{st}} \le t \le t_{\text{en}}, \end{aligned} \tag{4.8}$$

is determined together with the value of functional (3.2)

$$J[u_1(t), u_2(t)]. \tag{4.9}$$

at the end of the trajectory on hypersurface (3.1). We present functional (3.2) with changed control functions $u_{1c} = u_1(t) + \Delta u_1(t)$ and $u_{2c} = u_2(t) + \Delta u_2(t)$ in the following form:

$$J[u_1(t) + \Delta u_1(t), u_2(t) + \Delta u_2(t)]. \tag{4.10}$$

The difference between (4.10) and (4.9)

$$\begin{aligned} \Delta J = J[&u_1(t) + \Delta u_1(t), u_2(t) + \Delta u_2(t)] \\ &- J[u_1(t), u_2(t)] \end{aligned} \tag{4.11}$$

is computed by using equations (4.3)–(4.7) for costate variables.

Substituting the initial control $u_1 = u_1(t)$ and $u_2 = u_2(t)$ and trajectory (4.2) corresponding to it into the right-hand side of (4.3), we integrate it with boundary conditions (4.4) and taking (4.6) and (4.7) into account with reversed time and compute the vector-valued function of costate variables

$$\begin{aligned} p(t) = \{&p_T(t), p_{TS}(t), p_{Tr}(t), p_{VS}(t), \\ &p_{Vr}(t), p_{\eta 1}(t), p_{\eta 2}(t)\}, \quad t_{\text{st}} \ge t \ge t_{\text{en}}. \end{aligned} \tag{4.12}$$

With the help of (4.8) and (4.12), the change of functional (4.4) in the problem considered is determined as follows

$$\Delta J = \Delta J_1 + \Delta J_2 + o[\Delta J_1, \Delta J_2], \tag{4.13}$$

where

$$\begin{aligned} \Delta J_1 &= -\int_{t_{\text{en}}}^{t_{\text{st}}} c_1 p_{\eta 1}(t)\Delta u_1(t)dt, \\ \Delta J_2 &= -\int_{t_{\text{en}}}^{t_{\text{st}}} c_2 p_{\eta 2}(t)\Delta u_2(t)dt \end{aligned} \tag{4.14}$$

and $o[\Delta J_1, \Delta J_2]$ is an error, determined by a higher order infinitesimal than ΔJ_1 and ΔJ_2.

For the nonlinear system (1.1), the method of successive improvement of control guarantees success, if the following two conditions are met: (1) the trajectory at the current iteration is not extremal and (2) the change of the controlling variables is sufficiently small.

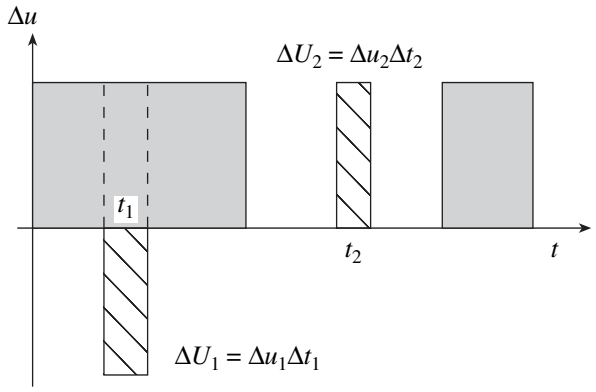

Fig. 6. Control change quanta in the successive approximation algorithm.

For our problem, the validity of the first condition is determined by the possibility of improving the value of the functional. The absence of this possibility in the case when all procedures of the algorithms are correct is the criterion of stopping the iteration process of control improving. The validity of the second condition, i.e., exceeding the error by the principal terms of (4.3), is provided experimentally by testing the change of the functional of (4.11) by using (4.13).

4.3. The Quantum Locally Optimal Algorithm of Successive Improvement of the Control

The effective use of formula (4.13) requires arranging both the choice of the magnitude of the change of the control and the localization of these changes rationally. In the algorithm constructed, the smallness of the change of the control was provided by their localization on small time intervals Δt_1 and Δt_2, so that the magnitudes of the changes ΔJ_1 and ΔJ_2 turn out to be proportional to the *control quanta*

$$\Delta U_1 = \Delta u_1 \Delta t_1, \quad \Delta U_2 = \Delta u_2 \Delta t_2. \tag{4.15}$$

After substituting control quanta (4.15) in expressions (4.14), they take the following form

$$\Delta J_1 = -c_1 p_{\eta 1}(t_1)\Delta U_1, \quad \Delta J_2 = -c_2 p_{\eta 2}(t_2)\Delta U_2. \tag{4.16}$$

Formula (4.16) shows that the magnitudes of the changes ΔJ_1 and ΔJ_2 for fixed values of quanta (4.5) are determined by the values of functions $p_{\eta 1}(t)$ and $p_{\eta 2}(t)$ at time instants t_1 and t_2 by introducing control quanta (4.15). These time instants should be chosen from the condition

$$\begin{aligned} \Delta J_1 &= \max_{t_1}[-c_1 p_{\eta 1}(t_1)\Delta U_1], \\ \Delta J_2 &= \max_{t_2}[-c_2 p_{\eta 2}(t_2)\Delta U_2]. \end{aligned} \tag{4.17}$$

Introduce the following notations:

$$\begin{aligned} Q_1 &= \max_{t \in [t_н, t_к]} [c_1 p_{\eta 1}(t)(2u_1(t) - 1)], \\ t_1 &= \arg\max_{t \in [t_н, t_к]} [c_1 p_{\eta 1}(t)(2u_1(t) - 1)], \\ Q_2 &= \max_{t \in [t_н, t_к]} [c_2 p_{\eta 2}(t)(2u_2(t) - 1)], \\ t_2 &= \arg\max_{t \in [t_н, t_к]} [c_2 p_{\eta 2}(t)(2u_2(t) - 1)]. \end{aligned}$$

Taking into account the fact that the control quanta (4.15) may take positive and negative values (see Fig. 6), depending on the current control $u_1(t)$ and $u_2(t)$, their magnitudes providing the validity of conditions (4.17) are determined by the formulas

$$\begin{aligned} \Delta U_1 &= \begin{cases} [1 - 2u_1(t_1)]\Delta t_1, & \text{if } Q_1 > 0, \\ 0 \text{ otherwise;} \end{cases} \\ \Delta U_2 &= \begin{cases} [1 - 2u_2(t_2)]\Delta t_2, & \text{if } Q_2 > 0, \\ 0 \text{ otherwise.} \end{cases} \end{aligned} \tag{4.18}$$

The computational experiments have shown that, for the regular convergence of the improvement iterations, controlling quanta (4.15) should satisfy the inequalities $|\Delta U_1| \le 1/5$ and $|\Delta U_2| \le 1/5$. The value $\Delta t_{1,2}$ is chosen corresponding to the integration step of system (1.1) and (1.3) by the fourth-order Runge—Kutta method.

From the point of view of iterative improvement of the treatment program, algorithm (4.18) means that at each iteration, for each 1/5 of a day, the decision to choose one out of three alternatives is made for each medication: (1) not to change the prescription, (2) to prescribe the medication, and (3) to cancel the medication.

5. THE RESULTS

In order to compare it with the uncontrolled regiment, the problem of the optimization of the treatment program was solved with the same initial conditions on the phase coordinates (presented in Fig. 3) The numerical method of solution, guaranteeing attaining the local maximum of the optimized functional, does not guarantee obtaining a global maximum. Therefore, the problems were solved with different initial approximations, which were taken as the no-treatment regime (Fig. 3) and the continuous treatment regiment (Figs. 4, 5) considered above.

5.1. The Iterative Process Dynamics

The work of the optimizing algorithm is illustrated in Fig. 7, in which the successive approximations with an initial control $u_1(t) \equiv u_2(t) \equiv 1$ are shown which cor-

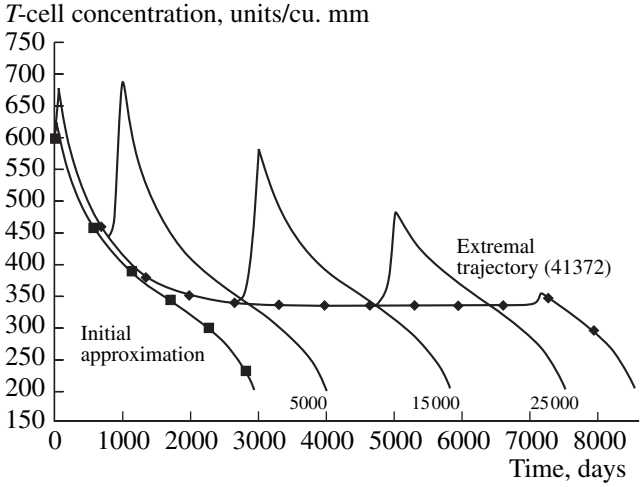

Fig. 7. *T*-cell dynamics graph modifications with iteration number increase.

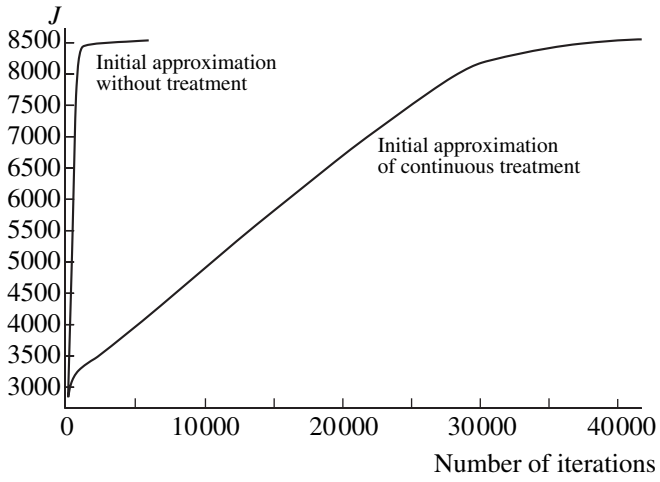

Fig. 8. The character of patient lifetime change with iteration number increase.

responds to the constant treatment program (Figs. 4, 5). Figure 7 demonstrates the systematic improvement of the treatment program with an increase in the number of iteration. As was mentioned before, the nonlinear character of equations (1.1) allows us to improve the controlling program only for small control quanta, which leads to the necessity to use tens of thousands iterations in the computation process.

The improvement of values of the optimized functional with the increase in the number of iterations for two realization of the computational algorithm with different initial approximations mentioned here is shown in Fig. 8. This figure reflects the process of the convergence to the extremal value of the functional as the number of iterations increases. The actual stopping of the growth of the functional value is the criterion for termination of the iteration process.

5.2. Extremal Treatment Programs

In Figs. 9a and 9b, the extremal solutions computed for two initial approximation are presented: (a) with continuous treatment for 41 372 iterations, (b) without treatment for 5228 iterations.

The upper graphs show that the dynamics of computed extremal regimes of the course of the illness and the corresponding values of the lifetime of the patient are the same for both initial approximations. This allows us to hope that the extremal regimes found are optimal. Thus, optimization of the treatment program can postpone the time of the terminal stage of the disease coming by more than 15 years compared with the untreated disease and the continuous treatment program.

In the lower graphs of Fig. 9, the extremal treatment programs are presented. The controls computed by the quantum algorithm determine the relay regimes of prescribing–canceling medicines with a frequency increasing with the increase in the number of iterations in such a way that the resulting treatment programs have the form of a thousand-cog comb. In Fig. 9, the averaged values of these comblike graphs on a week interval, which illustrate the average intensity of prescribing medicines, are shown. However, strictly speaking, they cannot be regarded as directions. The average intensity mentioned here might be prescribed only in the case when it equals 0 or 1 on a relatively large time interval. Otherwise, a nonregularized comblike graph of prescription/cancellation of medicines is recommended.

The relay form of controls is used in the algorithm, because the information on the effect of a small dosage of medicine is unavailable. When this information will become available, the algorithm with discontinuous controls can be inserted into the successive approximation process, and other restrictions required in the real problems can also be taken into account.

The graphs of controls in Fig. 9 show that, while the phase trajectories practically coincide for different initial approximations, the graphs of the extremal controls differ. This is evidence of the low sensitivity of the functional to the change of controls near its extremal value, which makes the computing process much more complicated.

CONCLUSIONS

Naturally, the *methodical* solution based on the model cannot be a recommendation for practical usage. However, it illustrates the role that mathematical methods can play in solving complex problems in medicine.

The question of the necessity and timeliness of using such sophisticated methods for solving therapy problems, which is now limited by general recommendations so far, should be discussed. On one hand, deep

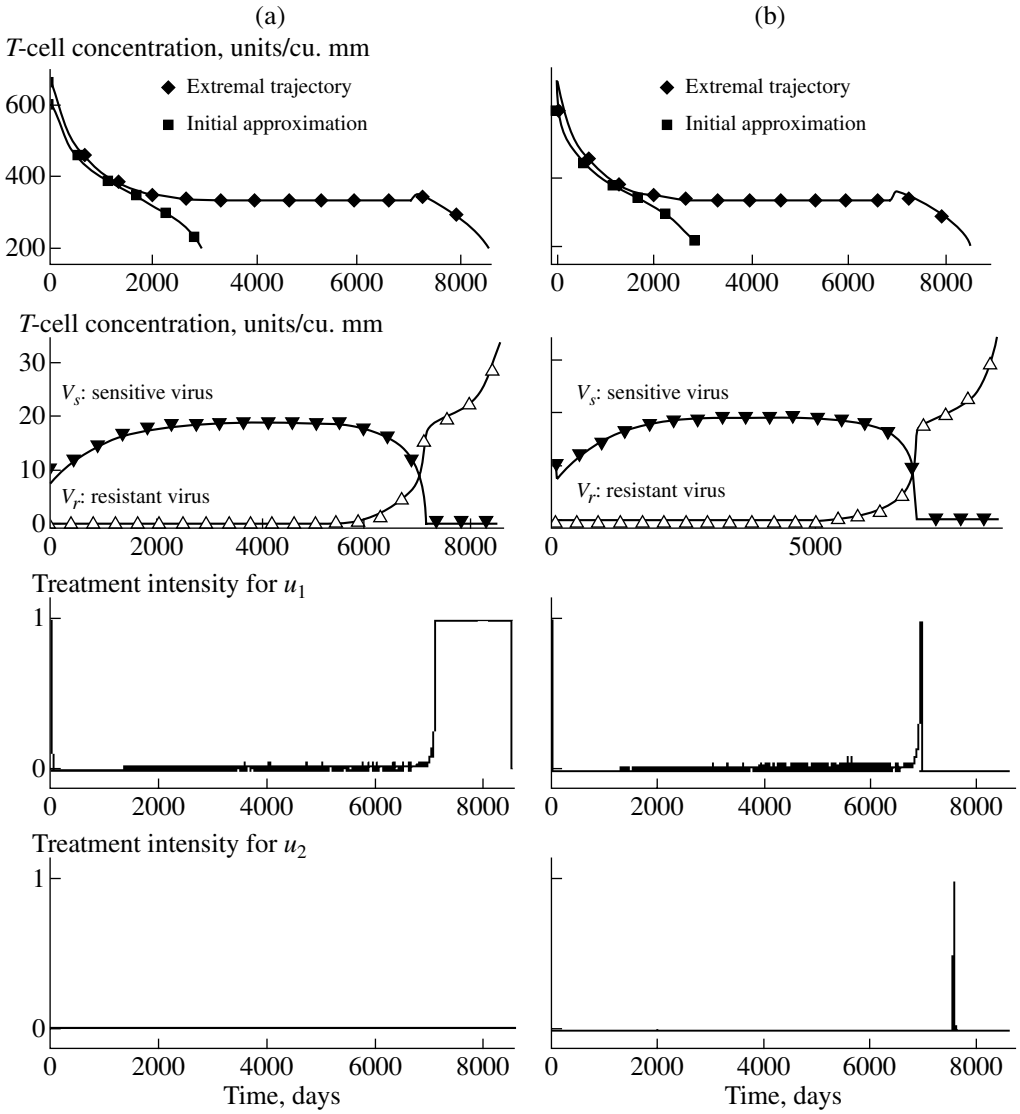

Fig. 9. Comparative dynamics of the initial and optimized treatment regiments for the initial approximations: (a) continuous treatment, (b) without treatment.

mathematization is premature, because there are no precise models of illnesses, and, on the other hand, the comparison of therapy with surgery, where the precision operations of the highest complexity (for example, transplantation of organs and extremities) have become common, allows us to assert that the application of precise methods in therapy has slipped seriously behind.

The pro et con arguments must be definite. This work shows the necessity and usefulness of applying rigorous mathematical methods in medicine (Table 2).

Table 2. Comparative data of controlled and uncontrolled treatment programs

Treatment program and its graph	Volume of medication		Amount of virus at the end, units/cu. mm	Lifetime, days
	First	Second		
No treatment (Fig. 3)	0	0	10022	2864
Constant treatment (Figs. 4,5)	3500	3500	8138	2931
Extremal program 1 (initial regime with continuous treatment, Fig. 9a)	1580.6	0	34	8530
Extremal program 2 (initial regime without treatment, Fig. 9b)	229.2	21	34	8530

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