USING ARTIFICIAL INTELLIGENCE AND COMPUTER TECHNOLOGIES FOR DEVELOPING TREATMENT PROGRAMS FOR COMPLEX IMMUNE DISEASES

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ABSTRACT. This article deals with a methodology of using up-to-date mathematical and informational techniques to control the human immune system. Through the example of mathematically controlled HIV therapy, prospects are demonstrated for technologies that have never been used in medicine. The results indicate the possibility of significant advances in prolonging the life of HIV-infected people with the aid of mathematical technologies, which allow reducing the amount of chemotherapy.

1. Introduction

Section 3 of the present article demonstrates the two limiting regimes of the dynamic simulation of HIV infection caused by the human immunodeficiency virus. 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 in 7 years and 10 months without treatment, and, in the case of the maximal intensive treatment with two active medications during the entire period of the disease, it comes in 8 years. In other words, eight years of treatment yield a two months increase in the lifetime of a patient.

This result, dramatically unmasking the severe character of HIV infection, points out the difficulties frustrating medical science in the successful treatment of this mortal infection. Hence, the two principal problems are: (1) understanding the intrinsic reasons for such a low *actual* efficiency of recommended medications, and (2) finding a way to use these medications, no matter how inefficient they seem, to achieve the greatest possible effect. Both these problems are taken care of by the mathematical and information methods presented in this article.

The first problem can be approached through the analysis of HIV population dynamics in humans. This dynamics can be studied experimentally, although mathematical modeling and computer simulations appear much more effective, because in this way it takes only a few hours to obtain a detailed description of all the processes within the human organism for ten or more years ahead. Such analysis shows that medications that pharmacology has to offer are extremely effective *locally*. It takes about 20–30 days to almost completely suppress the viral population. However, HIV displays extreme variability, and the suppressed viral strain is successfully replaced by its modified form, which is resistant to the employed drugs. Thus, medications locally effective during the first month of treatment are rendered virtually ineffective globally.

The second problem (that of using all existing (and future) drugs with effect greater than prolongation of a patient's life for more than a few months) is also dealt with by mathematics and computers. The numeric solution came to us as an absolute surprise and rightfully belongs to *inherent artificial intelligence of a computer* learned in advanced mathematics. Earlier, we have shown the examples of *superhuman intelligence* of mathematics and computers [18]. It must be mentioned, however, that those examples as well as the problem of artificial intelligence in the large are based on preliminary *training*, that is to say, the computer is provided with superintelligence by man, the author of algorithms. In the case described in the present article, it is the other way around: the computer teaches man the ways for rational control

of a complex system. Moreover, the proposals of a computer have all the features of human intelligence: there is logic behind them, and they have theoretical value and even parallel cases in history.

What logic is there behind the computer's proposal? Having proven that direct virus suppression yields no result, the computer (being given a purely technological assignment to try to prolong a patient's life as much as possible by as few steps as it takes) virtually gropes its way to find the following solution. Since it makes no sense to launch direct attacks against the virus because HIV mutation results in two viral strains instead of one, it appears to be a good move to have these two enemies of the human organism *confront each other*. This means that one should not exterminate the initial fraction at the greatest possible rate so that there would not be spare room for the modified one. On the contrary, it is necessary to control the former population in such a way that firstly it would not rear its head, and secondly, it would not give living space to the latter population. At the same time, the modified population must be maintained at a level enabling it to compete with the initial one.

Let us consider the theoretical value of the computer's solution. The described logic entails, mathematically an extraordinarily complex game of a human organism battling two conflicting adversaries. Modern control theory has no special methods to solve a game theory problem of such complexity, given that the process is described by a system of nonlinear differential equations. Yet a computer has proved capable of seeing this problem and solving it in a way that has never been formalized. The accuracy and delicacy of its control over the conflict between the viral populations corresponds to the extreme complexity of the problem: the resulting treatment program prescribes for every fifth part of the day over the 23-year treatment interval whether or not the patient must take a certain dose of one or two chosen medications.

Historical and political parallels for such handling of enemies can be easily found in ancient and modern history: a country not strong enough to defeat all of its enemies together or one by one may benefit from a quarrel between the enemies.

The results of these experiments are presented in Sec. 6. The treatment programs allow prolonging the lifetime of the patient treated by the same medications up to 23 years. In this case, the total medication intake decreased approximately by a factor of 15, compared with the continuous treatment regime.

The solution presented in Sec. 6, 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 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 by manipulating complex formulas, iteration after iteration, it is impossible to deprive this "advocate of life" of the right to be called intelligent.

In medical science, for solving problems that may be compared in complexity to problems of interplanetary spaceship trajectory-tracking, the methods of control theory are indispensable; without them, it is *impossible* to cope with such formidable challenges to human health as HIV. Understanding this situation should reduce the time needed to put these mathematical instruments into practice, instruments that exact sciences spent great effort and centuries to create.

This paper pursues methodical objectives: we do not profess to solve actual HIV infection problem but intend to demonstrate the opportunities that mathematical methods of control offer. Therefore, the medical and biological justifications of mathematical models of HIV infection dynamics are accepted without discussion. The methods considered 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 infection and in response to the creation of new medications. Another area of application is the systems of express-approbation 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.

2. Basic Description of the Immune System

This section presents a brief review of the immune system and its interaction with HIV necessary to understand the studied mathematical model.

2.1. Functioning of the Immune System. Whenever a foreign substance (*antigen*) finds its way into a human organism, an immune response is triggered. First, the antigen is met by *macrophages*, namely, cells that analyze all foreign particles, handing the results of their analysis over to a special class of T-lymphocytes (CD4+ T-cells) or T-cells.

There are two kinds of T-cells. T-cells of the first kind, generally known as *T-helpers* (normal concentration is about 1000 cells per cubic millimeter of blood), are decision-makers in the process of primary immune response. If they deem that the reaction of the immune system is necessary, they start to reproduce intensively, thus strengthening the immune system.

For the *cellular immune response* after interaction with the antigen, the immune system produces T-cells of the second kind (CD8+ T-cells), known as T-killers. Having received antigen-specific information, they search for and kill all the cells infected by the antigen.

For the *humoral immune response* (antibody response), T-helpers excite another kind of cells, called B-lymphocytes (B-cells). These cells in turn generate antigen-specific molecules of antibodies, serving as a weapon against the antigen.

If the immune response is successful, a certain part of each kind of cells retains information on the antigen. These cells are called *memory cells*. They form a knowledge base that helps to launch a much faster and rigorous immune response, when the same antigen or its sibling is once again found in the organism.

2.2. HIV Infection. Like all viruses, HIV does not reproduce itself without a host cell. Viruses usually insert copies of their DNA into the DNA of the host. Thus, when the host-cell is stimulated to proliferate, it reproduces copies of the virus.

HIV reproduces only through hosts of a certain nature. The protein on the virus' surface is similar to the protein on the T-cells' surface. Thus, having entered a human organism, HIV heads directly for the T-cells. Binding takes place, and HIV penetrates the host T-cell (Fig. 1 shows the life-cycle of HIV).
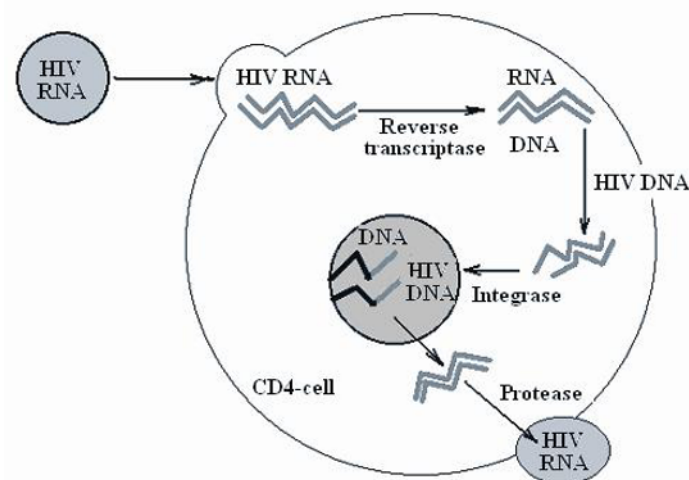

Fig. 1. HIV life cycle

HIV, being a retrovirus, unlike most viruses primarily installs its RNA rather than DNA into the host cell. It takes a special enzyme (a reverse transcriptase) to transcribe viral RNA into DNA. This DNA copy is then integrated into the DNA of the infected cell. The viral DNA, called the provirus, is then duplicated with the cell's DNA every time the cell divides. Stimulation of the T-cell by antigen leads to the production of new viral particles that bud from the surface of the infected cell. A more detailed description of the HIV life cycle may be found in [7, 12].

T-cells play a key role in the immune response, and this explains the devastating effect of HIV on the immune system. The impact of the depletion of T-cells on the human organism is that although the natural killer cells may be fit to perform their function of eliminating infection, they are never deployed. This then culminates in a clinical problem wherein the patient becomes vulnerable to infections that a healthy immune system would normally handle.

2.3. Four Stages of HIV Infection.

Incubation period. This period takes 2 to 4 weeks [12] from the time of initial infection to the first clinical manifestations of the disease. Immediately after infection HIV starts penetrating into cells that carry the CD4-receptor. In the typical course of HIV infection, the incubation period culminates in the clinical manifestation—an acute primary infection.

Period of primary clinical manifestations (acute infection). It continues for 5 to 44 days, having a large variety of symptoms. In the first 7–9 days the abrupt decrease of the numbers of both CD4- and CD8-lymphocytes is observed. Toward the end of the second week, the CD8-cell concentration increases. HIV antibodies can be detected a week after the beginning of acute infection [12].

Latent period. After the primary manifestations, in most cases, a relatively stable period starts, wherein millions of new copies of the virus are produced and almost all of them are killed by the immune response. This latent period may continue as long as several years. The level of CD4-lymphocytes gradually decreases at this stage of infection. One of the critical points is the fall of the T-cell concentration below 500 units per mm^3. Throughout the entire latent infection period the immune system puts up a desperate struggle against HIV, which normally ends with a great loss of CD4-cells, shortening of their lifespans, and malfunctions of the immune system. As a result, a decrease in immunity brings about the development of opportunistic infections.

Progression to immune deficiency (acquired immune deficiency syndrome). This final stage of HIV infection is called AIDS. It manifests itself by lethal complications in the form of multiple opportunistic infections and various neoplasm. The opportunistic infections are caused by pathogenic microorganisms that acquire insuperable aggressiveness under the condition of the immunity depression. Not a single tissue, organ or system of the patient is secure from their action. All this explains the extreme variety of clinical manifestations of AIDS.

2.4. Medical Treatment. Intensive research is carried out all over the world to find effective medications for HIV infection. This research is mainly directed on finding antiviral drugs to check HIV at different stages of its reproduction, or to recover the violated functions of immune system.

One of the promising ways is using a drug to block reverse transcriptase, the enzyme that helps to form HIV's DNA. Azidothymidine (AZT), for example, became the first of such drugs [6]. It is believed that AZT chemotherapy increases by a year the mean time of a patient's life at the AIDS stage. However, AZT is toxic; the bone marrow, for instance, suffers from it, which leads to anemia. Many drugs are still in the stage of clinical tests.

It is possible to design effective antiviral drugs, but this is frustrated by the variability of HIV. Within one organism new strains of HIV are formed continuously. HIV quickly develops drug resistance, and once effective drugs become useless. For this reason, the simultaneous use of several antiviral drugs (intensive multidrug therapy) is considered the best treatment policy.

3. The Model of HIV Infection Dynamics

3.1. Immune System Modeling. The problems of using mathematical simulation and control methods in biology and medicine were formulated by Norbert Wiener, the patriarch of cybernetics [23]. Mathematical models of the human immune system were constructed and studied in a number of publications of Russian and foreign authors [1, 2, 10, 11, 21, 22]. Mathematical models of immune system interaction with HIV are studied in [21, 22]. Some problems of optimization of immune processes including HIV infection were considered in [3, 4, 8, 9, 14, 15].

In this paper, we set up and solve the problem of optimal control of HIV infection treatment based on the mathematical model of [22]. 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 et al. [12].

3.2. The Controlled Model of HIV Infection. The modified control model constructed based on the uncontrolled model of [22] is described by the system of ordinary differential equations

$$
\begin{aligned}
\frac{dT(t)}{dt} &= S_1 - \frac{S_2 V(t)}{B_s + V(t)} - \mu_T T(t) + \frac{\lambda_1}{C + V(t)} T(t)V(t) - \big(\eta_1(t)k_s V_s(t) + k_r V_r(t)\big)T(t), \\
\frac{dT_s(t)}{dt} &= \eta_1(t)k_s V_s(t)T(t) - \mu_{T_i} T_s(t) - \frac{\lambda_2}{C_i + V(t)} T_s(t)V(t), \\
\frac{dT_r(t)}{dt} &= k_r V_r(t)T(t) - \mu_{T_i} T_r(t) - \frac{\lambda_2}{C_i + V(t)} T_r(t)V(t), \\
\frac{dV_s(t)}{dt} &= (1-q)\frac{\lambda_3}{C_i + V(t)} T_s(t)V(t) - k_V T(t)V_s(t) + \eta_2(t)\frac{G_s V_s}{B + V(t)}, \\
\frac{dV_r(t)}{dt} &= \frac{\lambda_3}{C_i + V(t)} T_r(t)V(t) + q\frac{\lambda_3}{C_i + V(t)} T_s(t)V(t) - k_V T(t)V_r(t) + G_r\big(V(t)\big)\frac{V_r(t)}{B + V(t)}, \\
\frac{d\eta_1(t)}{dt} &= c_1(1 - \eta_1(t) - u_1), \\
\frac{d\eta_2(t)}{dt} &= \frac{c_2}{1 - c_3}\big(1 - \eta_2(t) + u_2(c_3 - 1)\big).
\end{aligned}
\tag{3.1}
$$

The first five equations of system (3.1) repeat the equations of the model of [22] 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 [13] and numerical optimization methods [16, 17].

System (2.1) includes seven phase variables T, T_s, T_r, V_s, V_r, η_1, η_2. T is the concentration of uninfected T-cells. 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 immunodeficiency virus V_r, resistant to chemotherapy.

The immunodeficiency virus'es specific feature is its mutation ability. When treated by chemotherapy, the virus develops defensive mechanisms counteracting the action of the medications. This effect is called resistance, and the virus resulting from the 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 total virus population at the time t.

It is assumed that the resistant virus starts to come into the system from an external source (lymphoid system) only after the entire virus population achieves a certain threshold concentration (the last term of the fifth equation). 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

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the sensitive virus also begins to be replaced by the resistant one. In system (3.1), this effect is described by a discontinuous function G_r:

$$G_r(V) = \begin{cases} 0 & \text{if } V < V_0, \\ G_s & \text{if } V \geq V_0. \end{cases} \tag{3.2}$$

The treatment functions η_1 and η_2 in the uncontrolled model [22] are defined as functions of time and describe the effect of two antiviral drugs on the system. The first function describes the decrease in the last term of the first equation, reflecting the effect of T-cell infection 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.

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 (3.1), the sixth and seventh differential equations are introduced. Here, the control variables u_1 and u_2 (the treatment switches) are introduced, which may take values of 0 and 1. If $u_1 = 1$ and $u_2 = 1$ the chemotherapy is "on," if $u_1 = 0$ and $u_2 = 0$ it is cancelled.

A more detailed description of the model is presented in [3, 22]. For numerical simulation with system (3.1) the values of the constants of the model [22] are used, which are given in Table 1.

Table 1

Parameter	Description	Value
μ_T	mortality rate of uninfected CD4+ cells	0.005/day
μ_{T_i}	mortality rate of infected CD4+ T-cells	0.25/day
k_s	rate CD4+ T-cells are infected by sensitive virus	0.0005 mm^3/day
k_r	rate CD4+ T-cells are infected by resistant virus	0.0005 mm^3/day
k_V	rate of virus loss due to the immune response	0.0062 mm^3/day
λ_1	production rate of uninfected CD4+ T-cells	0.025/day
λ_2	production rate of infected CD4+ T cells	0.25/day
λ_3	production rate of virus in the blood	0.8/day
G_s	external lymphoid sensitive virus source constant	41.2 mm^3/day
G_r	external lymphoid resistant virus source constant	41.2 mm^3/day
V_0	threshold value for remission	0.5/mm^3
q	proportion of drug-resistant virus produced from wild-type virus	10^{-7}
C	half saturation constant of uninfected CD4+ T-cells	47.0/mm^3
C_i	half saturation constant of infected CD4+ T-cells	47.0/mm^3
B	half saturation constant of external virus input	2.0/mm^3
B_s	half saturation constant of CD4+ T-cell source	13.8/mm^3
S_1	source of CD4+ T-cells in the absence of the disease	4.0 mm^3/day
S_2	reduction constant of CD4+ T-cell source	2.8 mm^3/day
c_1	treatment parameter for suppression of the rate of CD4+ T-cell infection by virus	0.5
c_2	treatment parameter for suppression of the rate of virus contributed by the external lymphoid compartment	0.025
c_3	treatment parameter for maximal suppression of virus contributed by the external lymphoid compartment	0.15

4. 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.

4.1. The Dynamics of HIV Infection without Treatment. Figure 2 shows the results of numerical integration of Eqs. (3.1) without treatment. The solution corresponds to the values of $\eta_1(t) \equiv 1$, $\eta_2(t) \equiv 1$, and the constant values of switches $u_1(t) \equiv 0$, $u_2(t) \equiv 0$.
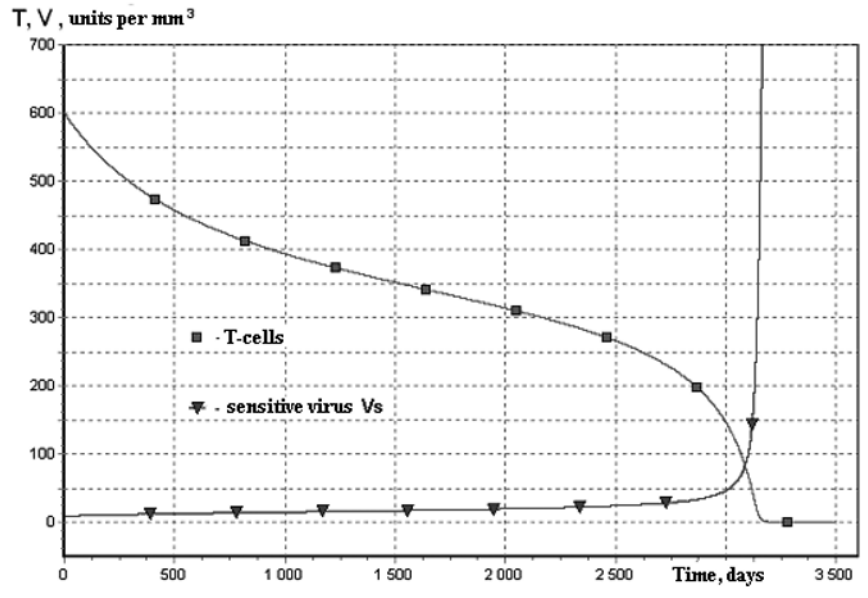
Fig. 2. HIV infection dynamics without therapy. Initial conditions: $T(0) = 600$ units per mm^3, $T_s(0) = 0$ units per mm^3, $T_r(0) = 0$ units per mm^3, $V_s(0) = 10$ units per mm^3, $V_r(0) = 0$ units per mm^3, $\eta_1(t) \equiv 1$, $\eta_2(t) \equiv 1$.

The graphs of Fig. 2 agree with the clinical data [21, 22]. During the first several weeks after the period of acute infection, the amount of T-cells falls gradually from 600–800 units per mm^3 almost 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 mm^3).

4.2. The Dynamics of HIV Infection in the Case of Continuous Treatment. In this case, the mutation mechanism of the virus is triggered. As a result, two stages in the dynamics of the process are distinguished: fast mutation and the subsequent relatively slow progression of the disease. In Eqs. (3.1), this regime corresponds to the constant values of switches $u_1(t) \equiv 1$, $u_2(t) \equiv 1$.

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 [22] and corresponds to the data of clinical observations. The dynamics of the process are illustrated in Fig. 3, in which the results of the numerical integration of Eqs. (3.1) with the same initial conditions as in Fig. 2 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 Eqs. (3.1) in the case of continuous treatment for a long period of time are presented in Fig. 4.

A comparison of Figs. 4 and 2 shows that they actually differ by a short interval of rapid dynamics (Fig. 3), after which the treatment has no effect on the modified resistant virus. As a result, the continuous
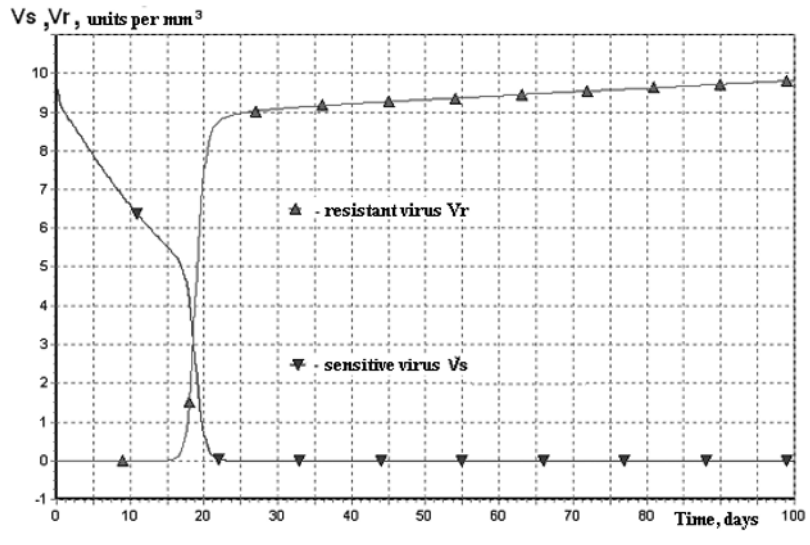
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Fig. 3. HIV infection dynamics under constant therapy during the first 100 days. Initial conditions are the same as for Fig. 2.
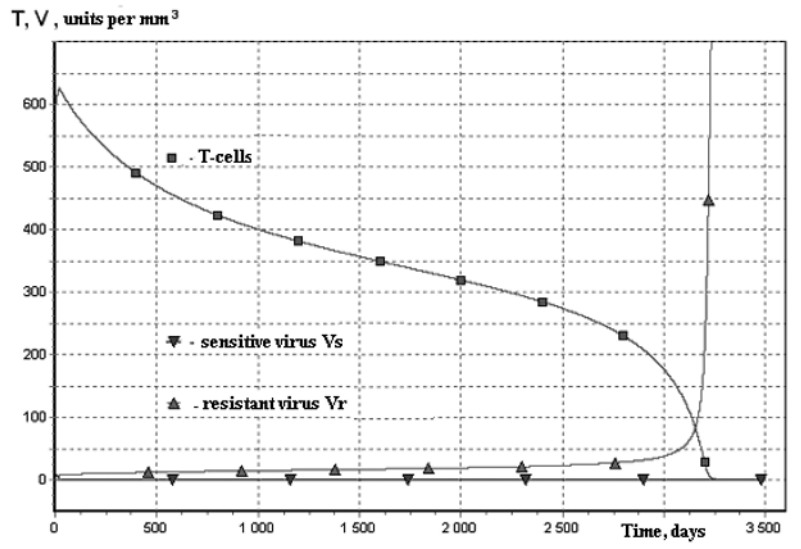

Fig. 4. HIV infection dynamics under constant therapy during the first 3500 days. Initial conditions are the same as for Fig. 2.

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 mm^3 in the concentration of T-cells) in just 66 days.

5. Formulating the Mathematical Problem of Optimal Control of the Treatment Process

In the statement of the mathematical problem of optimization, we used the recommendations developed by the Committee of the International AIDS Society [5]. From the viewpoint of optimal control, these recommendations are discussed in our earlier works [19].

The results of modeling of limiting regiments with and without application of chemotherapy point out the extremely high resistance of the virus to medications. The qualitative analysis of the complex

nonlinear model (3.1) does not even provide the possibility to point out the direction of modification of the continuous treatment program at least, since the control is already located at the boundary of the feasible domain, and it seems obvious that any decrease in the amount of medications cannot improve the patient's condition. The development of treatment programs better than the continuous treatment is problematic, and this question can only be studied by means of numerical experiments with the model.

5.1. Life Prolongation Problem. The objective of therapy is the prolongation of the patient's life. 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 [12], three categories of severity of the illness are distinguished, according to the concentration level in units per mm^3: (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 (200 units per mm^3) is the natural boundary for the studied processes in the immune system. In the mathematical model, this means that, in a seven-dimensional phase space (3.1), one should consider its trajectories ending on the hypersurface

$$T(t) - T^* = 0, \quad T^* = 200 \text{ units per mm}^3. \tag{5.1}$$

The problem of prolongation of the patient's life is to provide that the immune system would achieve the boundary (5.1) as late as possible. In a formal setup, the objective functional J in the treatment the optimization problem should be the termination time

$$J[u_1(t), u_2(t)] = t_\mathrm{f} = \{t \mid T(t) = T^*\}, \tag{5.2}$$

when the trajectory of system (3.1) reaches hypersurface (5.1) for the first time.

Formula (5.2) points out that the value of the functional t_f is determined by the choice of controlling functions $u_1(t)$ and $u_2(t)$. Thus, the numerical algorithm should be designed to find the functions for which functional (5.2) attains its maximum value among all functions, bounded by the conditions $u_1(t) \in \{0, 1\}$, $u_2(t) \in \{0, 1\}$ for all $t \in [t_0, t_f]$:

$$J[u_1(t), u_2(t)] = t_\mathrm{k} = \{t \mid T(t) = T^*\} \to \max_{u_1(t), u_2(t)}. \tag{5.3}$$

The solution of the optimization problem with the objective function (5.2) will show how much to the right (in terms of the time axis) a computer can draw a patient's life trajectory. In order to compare the results of computer optimization to the initial limiting regimes let us solve the optimization problem with two more objective functions. These two problems will be solved on the same time interval as the initial regimes (3500 days), and their solutions will show how much a computer can improve the "quality" of the process in comparison with the full-treatment and no-treatment modes within the same time.

5.2. Terminal Objective Function. When it comes to numbers, the quality of an immune system is defined by the concentration of T-cells. Therefore, it is natural to take as a goal the highest possible value of T-cell concentration at the end of the control interval ($t_\mathrm{f} = 3500$ days). The formalized objective function for system (3.1) in this case is given by the terminal functional $J = T(t_\mathrm{f})$, and the problem consists in its maximization:

$$J = T(t_\mathrm{f}) \to \max. \tag{5.4}$$

5.3. Integral Objective Function. The solution of the optimization problem with the terminal objective function gives for the best T-cell concentration at the right end of trajectory. However, this setting of the problem allows for the dips in the graphs of the T-cell concentration in the middle of the extremal trajectory. Such dips signify the weakening of the immune system during the treatment process, in spite of the good outcome. This is undesirable from the viewpoint of the protection of the patient from the accompanying opportunistic diseases. For this reason, a problem arises of finding an objective function to maintain the T-cell concentration above a certain minimum value during the whole treatment period.

Let us consider the problem

$$J = \int \Phi(t)\,dt \to \min, \tag{5.5}$$

where

$$\Phi(t) = \begin{cases} [A - T(t)]^2 & \text{if } T(t) < A, \\ 0 & \text{if } T(t) \geq A \end{cases}$$

and the value of constant A is determined in the course of optimization (see [16]). The objective function (5.5) imposes a penalty on values of $T(t)$ below the boundary of A.

6. Results

The optimization problems were solved by a numerical method of successive improvements of the objective function (see [16, 17]) adapted to system (3.1). The detailed description of the algorithm is given in [19, 20]. The initial conditions for all the solutions are the same as for Figs. 2–4, which allows comparison of various treatment programs. The problems were solved with the no-treatment regime (Fig. 2) and the continuous treatment regime (Figs. 3 and 4) chosen as initial approximations.

6.1. Extremal Treatment Programs. Figure 5 shows the extremal solutions computed for two initial approximation: (a) with continuous treatment for 41,372 iterations, (b) without treatment for 5,228 iterations.
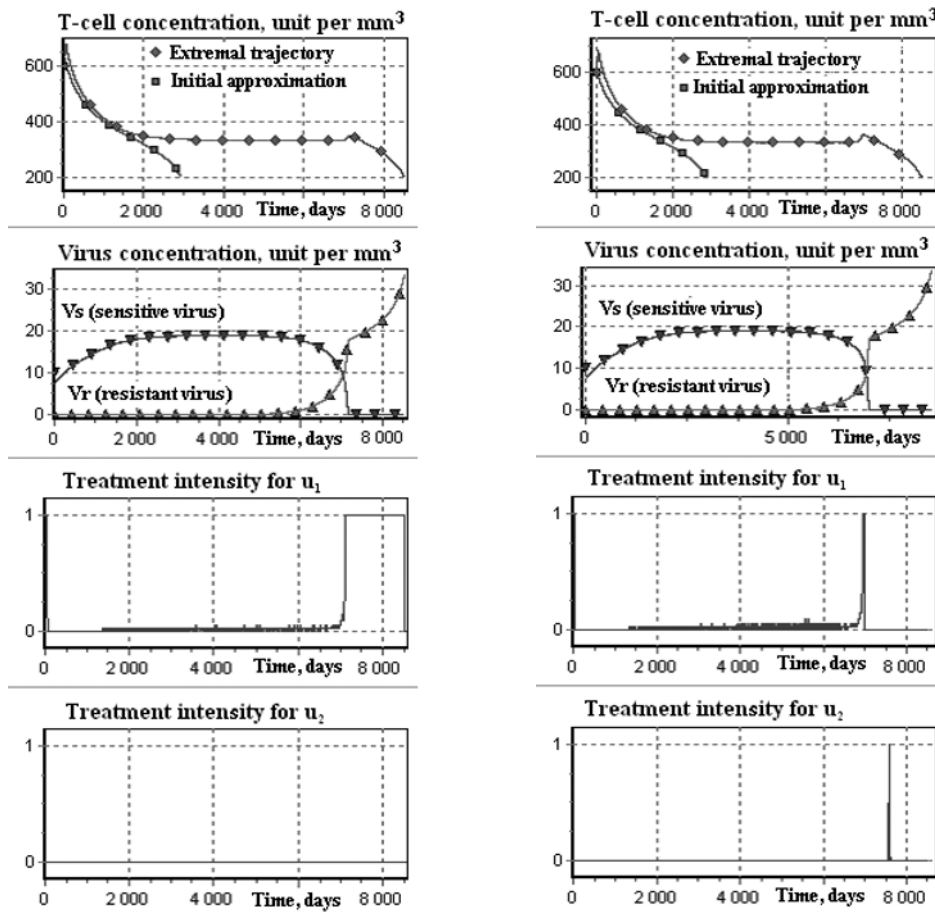

Fig. 5. Comparative dynamics of the initial and optimized treatment regimes for the initial approximations: (a) continuous treatment, (b) without treatment.

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 terminal stage of the disease by more than 15 years compared with the untreated disease and the continuous treatment program.

In the lower graphs of Fig. 5, the extremal treatment programs are presented. The control functions computed by the quantum algorithm determine the relay regimes of prescribing or canceling medicines, with the frequency increasing with increase in the number of iterations in such a way that the resulting treatment programs have the form of a comb with a thousand teeth. In Fig. 5, the averaged values of these comblike graphs on a weekly 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 where 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 control functions is used in the algorithm, because information on the effect of a small dosage is unavailable. When this information becomes available, the algorithm with discontinuous
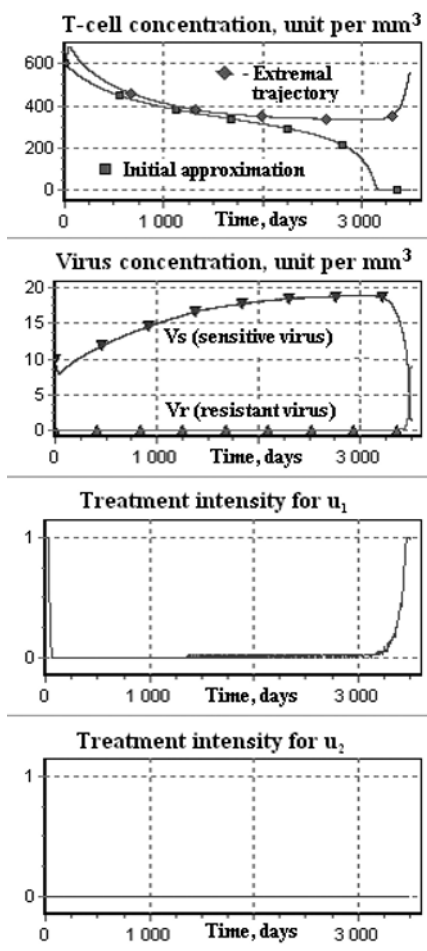

Fig. 6. Comparative dynamics of the initial and optimized treatment regimes: terminal objective function.
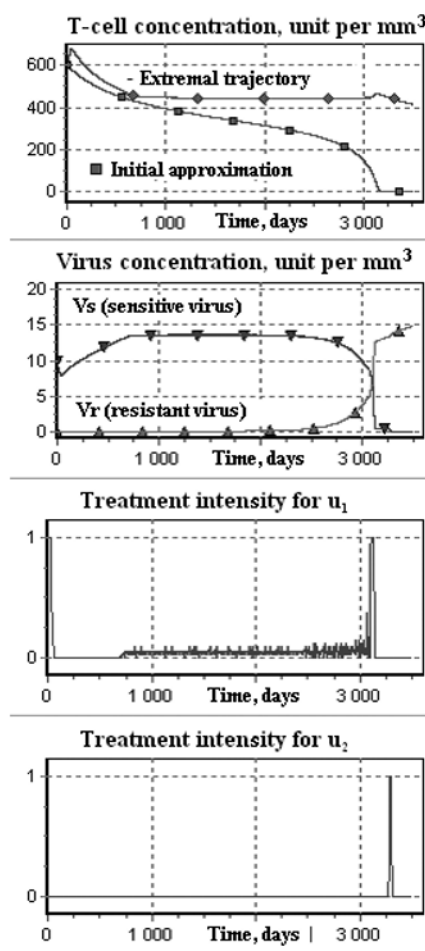
Fig. 7. Comparative dynamics of the initial and optimized treatment regimes: integral objective function ($T > 430$).

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 control functions in Fig. 5 show that, while the phase trajectories practically coincide for different initial approximations, the graphs of the extremal control functions differ. This is evidence of the low sensitivity of the functional to the change of control functions near its extremal value, which makes the computing process much more complicated.

Figures 6 and 7 show the extremal trajectories found by the computer for problems with terminal (5.4) and integral (5.5) objective functions, respectively. These results are obtained for the no-treatment regime as an initial approximation. It turned out that both objective functions have worse values for the extremal solution obtained for the permanent-treatment regime chosen for the initial approximation. This does not mean that the solution shown in Fig. 6 is necessarily optimal, because the method [16,17] guarantees only the fulfillment of necessary conditions of optimality and attainment of local extrema. However, all the solutions found for diverse initial approximations either proved worse than those shown in Figs. 6 and 7 or resulted in the same values of the objective functions.

Figure 7 presents the extremal trajectory for the problem with the objective function (5.5) and the value $A = 430$ units per mm^3. With this value of A the value of the objective function (5.5) equals zero, whereas with the greater value of $A = 435$ units per mm^3 the extremal value of the objective function exceeds zero, which means that there is no way to maintain the concentration of T-cells above the level of 435 units per mm^3.

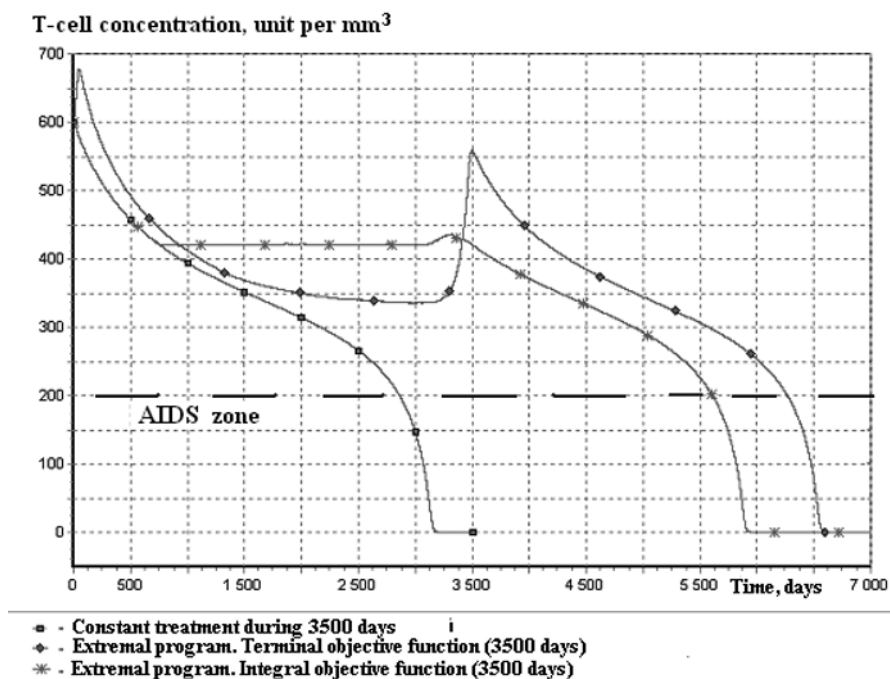The quantitative estimates of all treatment programs are listed in Table 2.

Fig. 8. T-cell dynamics for various treatment programs.

6.2. Logical Analysis of the Mathematical Solution of the Problem.

The solutions shown in the previous section are not common for standard problems of optimal control theory. Usually optimal solutions of such problems either correspond to the boundary of the feasible control domain or belong to the interior of this domain. For model (3.1) these boundaries are found in Sec. 3 and listed in Table 2: when the control variables take values from the lower boundary $u_1(t) \equiv 0$, $u_2(t) \equiv 0$ the patient lives 7 years, 10 months and 10 days; when the control variables take values from the upper boundary $u_1(t) \equiv 1$,

Table 2. Comparative data of controlled and uncontrolled treatment programs.

Treatment program and its graph	Number of iterations	Amount of medication, units		T-cells concentration at 3500th day, units per mm^3	Virus concentration at 3500th day, units per mm^3	Lifetime, days*
		First	Second			
No treatment (Fig. 2)	–	0	0	0.24	10022	2864
Constant treatment (Figs. 3, 4)	–	3500	3500	0.33	8138	2931
Extremal program 1 (initial regime with continuous treatment, Fig. 5a)	41372	1580.6	0	355	18.9	8530
Extremal program 2 (initial regime without treatment, Fig. 5b)	5228	229.2	21	355	18.9	8530
Extremal program 3 (initial regime without treatment, Fig. 6)	4830	180.2	0	560	10.28	6270
Extremal program 4 (initial regime without treatment, Fig. 7)	5786	200.2	23.6	430	15.1	5548

* Lifetime is defined as the number of days before the T-cell trajectory goes below 200 units per mm^3. For programs 3 and 4, for which treatment ended on the 3,500th day, the trajectories were continued to the right without treatment.

$u_2(t) \equiv 1$ the patient lives up to 8 years and 11 days. For a standard problem it would be expected that a decrease in chemotherapy will reduce the patient's life, which will fall within the two-month interval between the two limiting regimes. However this hypothesis is paradoxically refuted by the optimization results as shown in Table 2: the patient's life *increases* by decades.

The reason for this phenomenon lies within the intricacies of the calculations carried out by the computer, but the mathematical descriptions must be translated into words for human comprehension. For such translation let us have a closer look at one more system of graphics, given by Figs. 9 and 10.
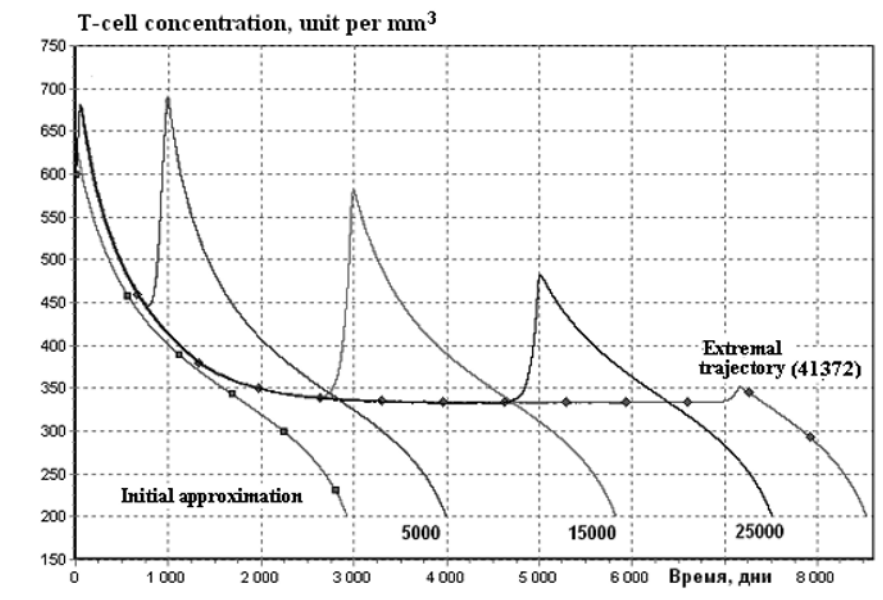

Fig. 9. T-cell dynamics graph modifications with iteration number increase.
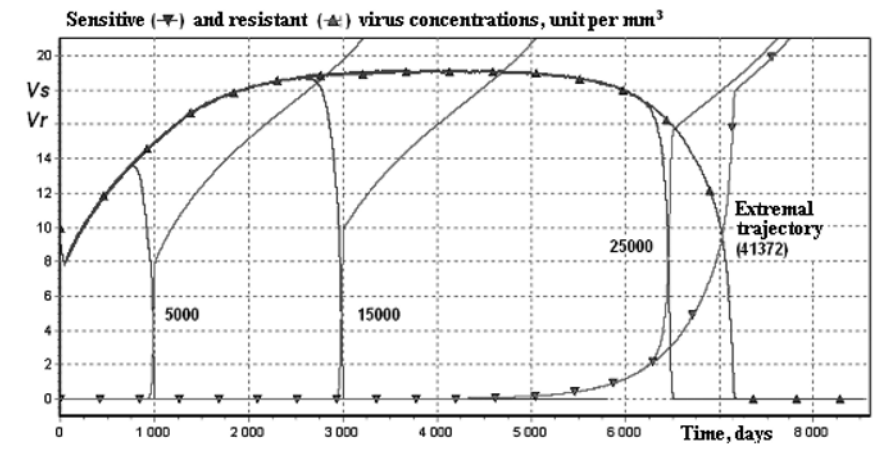
Fig. 10. Sensitive and resistant virus dynamics graph modifications with iteration number increase.

The former of these graphics shows the changes that a T-cell concentration trajectory (which, in fact, is a life trajectory) undergoes as the number of the algorithm's iteration grows. The latter, Fig. 10, explains why this trajectory changes in such a way. The reason for this is the cleverness of the computer, which delays the moment of the sensitive virus'es ultimate suppression and, consequently, the time when the population of resistant virus comes to power. The result of this very fine, minute, noble, and intellectual work of the computer (which took from 5000 to 45000 iterations) is summarized in Table 2. In fact, the computer's own logic essentially expanded the limitations imposed on the problem by the formal mathenatical algorithm.

Conclusion

Naturally, the methodical solution based on the model cannot be recommended for practical use. 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 to general recommendations so far, should be discussed. On the one hand, deep mathematization is premature, because there are no precise models of illnesses, and, on the other hand, comparison of therapy with surgery, where precision operations of the highest complexity (for example, transplantation of organs and limbs) have become common, allows us to assert that the application of precise methods in therapy has fallen seriously behind.

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