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Optimization of infectious disease processes modelled by nonlinear delay differential equations

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In this paper the numerical approach to the solution of optimization problems of processes which are modelled by nonlinear delay differential equations (DDEs) with constant delays is presented. Based on DDEs solution the different characteristics of the modelled process are calculated. One of them is selected as the objective functional. Other characteristics can play a role of constraints. The control is made by the functions, which define the coefficients of DDEs. As a result of piece-wise-linear approximation of control function the non-linear mathematical programming problems are obtained. The efficiency of the software developed for solution of nonlinear DDEs and optimization of DDE systems is illustrated on the infectious disease process model.

Keywords: delay differential equation, optimization, non-linear programming problem, infectious disease process.

Introduction. Delay differential equations (DDEs) are used to model a variety of phenomena in the physical and natural sciences. Also time delays which occur in the modelling of biological systems can be modelled using DDEs. Successful application of mathematical models of real-life processes is closely connected with development of the appropriate algorithms and software.

The mathematical models, developed by Marchuk [1] for modelling of the processes in the immune system of an organism infected with infectious diseases are considered in the paper. Mathematical model of a disease, data bases of the clinical and laboratory observation of the disease process dynamics for another patient with the same disease and data base of the patient (which permanently is filled up during the treatment process) are the basis for prediction of the disease process dynamics. In addition to the prediction of disease process dynamics the problems connected with optimal control of these processes and with substantiating the recommendations for optimal therapy of the patient remain actual. The aim of this paper is formulation of optimal control problems of the treatment process of an infectious disease, creating appropriate algorithm and software.

1. Mathematical models of an infectious disease

In general the process of a disease is described by the system of nonlinear differential equations with delay [1-3]

$$y'(t) = f\left(t, y(t), \tilde{y}(t-\tau), g, u(t)\right), \qquad t_0 \le t \le t_e, \tag{1}$$

where $y(t) = \left(y_1(t), ..., y_k(t)\right)^{\mathrm{T}}$ is state function; $\tilde{y}\left(t-\tau\right) = \left(y_{i_1}\left(t-\tau_1\right), ..., y_{i_r}\left(t-\tau_r\right)\right)^{\mathrm{T}}$, $1 \le i_1, ..., i_r \le k$; y_{i_j}, $1 \le j \le r$ is component of the state function defined in the interval of delay $\left[t_0 - \tau_j, t_0\right]$; $\tau = \left(\tau_1, ..., \tau_r\right)^{\mathrm{T}}$ is vector of the delay interval; r is number of intervals of delay; $g(t) = \left(g_1, ..., g_l\right)^{\mathrm{T}}$ vector of given parameters of the model; $u(t) =$ $= \left(u_1(t), ..., u_s(t)\right)^{\mathrm{T}}$ is control function; $f = \left(f_1, ..., f_k\right)^{\mathrm{T}}$ is given function of the system.

System of equations (1) is added by initial conditions

$$y\left(t_0\right) = y_0, \quad y_{i_j}(t) = p_j(t), \quad t \in \left[t_0 - \tau_j, t_0\right], \quad j = \overline{1, r}, \tag{2}$$

where $p_j(t)$ is a given function in the interval of delay.

Note, that the state function *y* depends on both independent variable *t* (usually time) and parameters of model *g* and control parameters *u*.

System of nonlinear differential equation with delay (1), (2) is solved by Dormand and Prince variable step method [4].

Let us consider the so-called simple mathematical model [1, 2]. Model of the disease in this case in dimensionless form can be presented as a system of four differential equations with delay

$$\begin{aligned}
&V'(t) = \left[g_1/\left(1 + g_9 u\right)\right]V - g_2 FV, \\
&F'(t) = g_4\left(C - F\right) - g_8 FV, \\
&C'(t) = \xi(m) g_3\left(1 + g_{10}u\right)V\left(t-\tau\right)F\left(t-\tau\right) - g_5\left(C-1\right), \quad t \in \left[t_0, t_e\right], \\
&m'(t) = g_6 V - g_7 m.
\end{aligned} \tag{3}$$

Here *V*(*t*), *F*(*t*), *C*(*t*) are concentrations of viruses (antigens), antibodies and plasma cells; *m*(*t*) is relative characteristic of the damaged organ; g_1, ..., g_{10} are parameters of the model; *u*(*t*) is control function which has an effect on the rate of virus multiplication (parameter g_1) and on the coefficient of the immune system stimulation (parameter g_3); τ is interval of delay, $\tau \in R$, $r = 1$. Function *u*(*t*) can be treated as the temperature of the patient body. The increase of temperature leads to reduction of the rate of virus multiplication. At the same time the temperature increase stimulates generation of plasma cells.

Multiplier $\xi(m)$ is the continuous non-increasing function which is chosen in the following form

$$\xi(m) = \begin{cases} 1, & m < g_{m1}, \\ g_{m2}\left(1 - m\right), & g_{m1} \le m \le 1, \end{cases} \tag{4}$$

where g_{m1}, g_{m2} are parameters of the model. Function $\xi(m)$ describes the dysfunction of the immune system due to the substantial organ damage.

System of equations (3) is supplemented with initial conditions

$$C(t_0) = C_0, \quad m(t_0) = m_0,$$
$$V(t) = \varphi_1(t), \quad F(t) = \varphi_2(t), \quad t \in [t_0 - \tau, t_0]. \tag{5}$$

2. Formulation of optimization problem

To construct the optimization model along with constructing the disease model it is necessary to select the control parameters among the model input parameters , to determine functional which explains the characteristics of the disease, to select the objective of the therapy and constraints which can not be disturbed during the treatment.

2.1. Characteristics of the disease. Denote by k_1, k_2, k_3 numbers of components of vector y which defines a concentration of viruses, antibodies and relative characteristic of the damaged organ, respectively. The following functionals [5-8] are calculated in this paper

$$\tilde{\varphi}_1(u) = \int_{t_1}^{t_2} y_{k_3}(t)\,dt, \quad \tilde{\varphi}_2(u) = \frac{\ln(y_{k_3}(t_1)) / \ln(y_{k_3}(t_2))}{t_3 - t_4},$$
$$\tilde{\varphi}_3(u) = \int_{t_0}^{t_e} y_{k_1}(t)\,dt \Bigg/ \left[(t_{\max} - t_0)\int_{t_0}^{t_e} y_{k_2}(t)\,dt + S_0\right], \quad \tilde{\varphi}_4(u) = \max_{t\in[t_5, t_6]} y_{k_3},$$
$$\tilde{\varphi}_5(u) = t_7, \quad \tilde{\varphi}_6(u) = t_9 - t_8, \quad \tilde{\varphi}_7(u) = \int_{t_{10}}^{t_{11}} y_{k_1}(t)\,dt, \tag{6}$$

where $\tilde{\varphi}_1$ defines the total damage of the organ in the interval $[t_1, t_2]$; $\tilde{\varphi}_2$ is average rate of functional recovery in the interval $[t_3, t_4]$; $\tilde{\varphi}_3$ is index of status of the immune system of the organism, which characterizes the rate of synchronization of several links of the immune system (S_0 is given parameter, $t_{\max}$ is time of achieving the maximum value of antibody concentration); $\tilde{\varphi}_4$ is maximum value of the damaged organ in the interval $[t_5, t_6]$. $\tilde{\varphi}_5$ is moment of recovery time, $y_{k_1}(t_7) < \varepsilon$, $\varepsilon \approx 10^{-15}$ (complete elimination of viruses from the body); $\tilde{\varphi}_6$ is interval of remission between regular stresses in case of chronic disease (t_9, t_8 are moments of the time when viruses achieve the maximum value; $t_9 > t_8$); $\tilde{\varphi}_7$ is total amount of viruses in the interval $[t_{10}, t_{11}]$.

2.2. Optimization problem. One of the functional $\tilde{\varphi}_1, ..., \tilde{\varphi}_7$ is selected as the objective of the therapy

$$\varphi_0(u) = \tilde{\varphi}_i(u), \quad i \in \{1, ..., 7\}.$$

Other functionals can play the role of constraints

$$\varphi_j(u) = \tilde{\varphi}_k(u) - \varphi_k^+ , \quad k \in \{1,...,7\} , \quad k \neq i, \quad j = \overline{1,M} ,$$

where φ_k^+ is feasible value of functional $\tilde{\varphi}_k$, M is quantity of constrains. Denote by $\tilde{U}_\partial = \left\{ u : u \in \tilde{U},\ \varphi_j(u) \le 0,\ j = \overline{1,M} \right\}$ a set of feasible value of control function, $\tilde{U}$ is a set of control function.

Optimal control of the problems of the immunotherapy consists of finding such a control function $u_*(t)$ of the treatment process which is the best (in sense of choosing the objective of the therapy) among feasible variants of the therapy

$$\varphi_0(u_*) = \inf_{u \in \tilde{U}_\partial} \varphi_0(u) . \tag{7}$$

2.3. Optimization problem as non-linear programming problem. In this paper the optimal control problem (7) using approximation of control function by piecewise polynomial function is transformed to the mathematical programming problem. Each of the components $u_i(t),\ i = \overline{1,s}$ of control function in the result of approximation can be presented as function $u_i(t) = u_i\left(t, \tilde{b}^{(i)}\right),\ \tilde{b}^{(i)} = \left(b_1^i,...,b_{n_i}^i\right)^{\mathrm{T}}$. Denote by $b = \left(b_1,...,b_n\right)^{\mathrm{T}}$ the vector of optimization parameters consisting of the components of vectors $\tilde{b}^{(i)}$, $i = \overline{1,s},\ n = n_1 + ... + n_s$. Let us assume that $U = \left\{ b : b^- \le b \le b^+, b, b^-, b^+ \in R^n \right\}$ is a feasible region. The value b^-, b^+ can be found from region $\tilde{U}$. Due to the approximation of control function the functionals (6) are functionals of optimization vector b. Then the optimal control problem (7) is formulated as a non-linear mathematical programming problem: find the vector of optimization parameters $b_* \in U_\partial$ such that

$$\varphi_0(b_*) = \min_{b \in U_\partial} \varphi_0(b) , \tag{8}$$

where $U_\partial = \left\{ b :\in U, \varphi_j\left(b\right) \le 0,\ j = \overline{1,M} \right\}$ is a feasible region.

Optimization problem (8) is solved by the combined method of penalty function and different direct search methods, gradient methods and conjugate gradient methods [9, 10].

Based on an algorithms elaborated for the solution of the direct problem (1)-(2) and the optimization problem (8), proper software for optimization of DDEs systems has been created in Delphi environment.

3. Results of optimization

Choosing different values of parameters $g_i,\ i = \overline{1,10}$ model (3)-(5) simulate four possible forms of infectious disease: acute form with recovery, chronic form, subclinical form and lethal outcome [1, 5]. In this paper the results of some optimization problems for acute form with recovery and chronic form of disease are presented.

3.1. Acute form of disease. The problems were solved for the following values of input parameters of the model (3)-(5) [1, 5]: $\tau = 0{,}5$; $t_0 = 0$; $t_e = 100$; $g_1 = 2$; $g_2 = 0{,}8$; $g_3 = 10000$; $g_4 = 0{,}17$; $g_5 = 0{,}5$; $g_6 = 10$; $g_7 = 0{,}12$; $g_8 = 8$; $g_9 = 1$; $g_{10} = 25$; $g_{m1} = 0{,}1$; $g_{m2} = 10/9$; $C(0) = 1$; $m(0) = 0$; $p_1(t) = \max(0, t + 10^{-6})$, $p_2(t) = 1$, $t \in [t_0 - \tau, t_0]$.

Variation of V, C, F, m with time in case $u(t) = 0$ (without control of the disease process) is presented in Fig. 1. Since high concentration of viruses is located in some interval $[t_a, t_b]$ it is advisable to search nonzero control function in this interval. In the examples of optimization problems presented in this paper, the interval [0; 20] is divided into $n = 4$ equal parts. In each part control function u is approximated by constant function.

The following optimal control problems are considered:

a) minimization of characteristic of the damaged organ $\tilde{\varphi}_1$ in interval $[t_0, t_e]$

$$\varphi_0(u) = \tilde{\varphi}_1(u) \to \min_u ,$$
$$\tilde{U}_\partial = \{u : 0 \le u(t) \le 1\} ; \qquad (9)$$

b) minimization of time recovery $\tilde{\varphi}_5$

$$\varphi_0(u) = \tilde{\varphi}_5(u) \to \min_u ,$$
$$\tilde{U}_\partial = \{u : 0 \le u(t) \le 1\} ; \qquad (10)$$

c) minimization of the characteristic of the damaged organ $\tilde{\varphi}_1$ in interval $t \in [t_0, t_e]$ with constraint on time of recovery $\tilde{\varphi}_5$

$$\varphi_0(u) = \tilde{\varphi}_1(u) \to \min_u ,$$
$$\tilde{U}_\partial = \{u : 0 \le u(t) \le 1,\ \varphi_1(u) = \tilde{\varphi}_5(u) - \varphi_5^+\}, \quad \varphi_5^+ = 10 . \qquad (11)$$

In Table 1 the initial values of functionals $\tilde{\varphi}_i$, $i = 1, 4, 5, 7$ (in this case $u(t) = 0$) and values of these functionals obtained as the result of the solution of optimization problems (9)-(11) are given. A sign (*) is placed next to the optimal value of functional

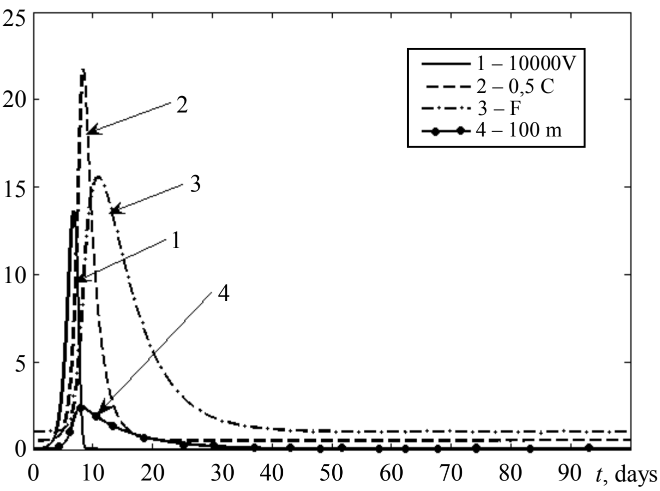

Fig. 1. Variation of V, C, F, m with time (acute form, $u(t) = 0$)

$\tilde{\varphi}_i$ if it is the objective functional. If functional $\tilde{\varphi}_i$ is included in the feasible region U_∂ the value of this functional is marked as (+). As a result of the problem (9) solution the value of the total damage of the organ (functional $\tilde{\varphi}_1$) is considerably decreased. At the same time the moment of time recovery (functional $\tilde{\varphi}_5$) is increasing.

In the issue of solution of optimal problem (10) the moment of the time of recovery (functional $\tilde{\varphi}_5$) decreases from 11,2 to value 7,5. At the same time (as expected) the value of $\tilde{\varphi}_1$ is greater than the optimal value of this functional when the problem (9) is solved.

We put the result of the solution of the optimization problem (11) in the last column of Table 1. Consequently the value of $\tilde{\varphi}_1$ is substantially lower to compare with the initial value of this functional (this value, as expected, is greater than the optimal value of this functional in problem (9)). At the same time the moment of the time of recovery is lower than its initial value.

Also in Table 1 the values of functionals $\tilde{\varphi}_4, \tilde{\varphi}_7$ are given. As expected, the values of these functionals are lower to compare with their initial values.

Table 1

Initial and optimal values of functionals $\tilde{\varphi}_i$, i = 1, 4, 6, 7 (acute form)

Number of functional, i	Initial value of functional $\tilde{\varphi}_i$	Optimal value of functional $\tilde{\varphi}_i$, problem (9)	Optimal value of functional $\tilde{\varphi}_i$, problem (10)	Optimal value of functional $\tilde{\varphi}_i$, problem (11)
1	$2{,}57\cdot10^{-1}$	$5{,}66\cdot10^{-3}$ (*)	$5{,}11\cdot10^{-2}$	$1{,}26\cdot10^{-2}$ (*)
4	$2{,}49\cdot10^{-2}$	4,93·10 – 4	$5{,}19\cdot10^{-3}$	$1{,}19\cdot10^{-3}$
5	11,2	16,4	7,15 (*)	10,0 (+)
7	$3{,}08\cdot10^{-3}$	$6{,}79\cdot10^{-5}$	$6{,}13\cdot10^{-4}$	$1{,}52\cdot10^{-4}$

In Table 2 the optimal values of optimization parameters $b_i, i = \overline{1,4}$ are presented. The values of b_2, b_3 are close to its upper bound. So it is necessary to increase the value of control function $u(t)$ (temperature) during the time of the acute condition of the disease (close to the peak of the disease).

Table 2

Optimal values of optimization parameters b_i, $i = \overline{1,4}$ (acute form)

optimization parameter	Optimal value of b_i, problem (9)	Optimal value of b_i, problem (10)	Optimal value of b_i, problem (11)
b_1	0,365	0,000	0,189
b_2	1,000	0,939	1,000
b_3	0,983	0,900	0,921
b_4	0,400	0,200	0,000

3.2. Chronic form of disease. In this case the values of all the parameters of the model (3)-(5) were the same as in the case of the acute form except the parameter g_6: $g_6 = 300$. Variation of V, C, F, m with time and without control of the disease process is presented in Fig. 2. In case of chronic disease the periodic process is obtained.

It becomes obvious that the treatment of the chronic form should widen the interval between the disease peaks. So, the optimization problem consists of maximization of the interval of remission between regular stresses of chronic disease

$$\varphi_0(u) = \tilde{\varphi}_6(u) \to \min_u ,$$
$$\tilde{U}_\partial = \{u : 0 \le u(t) \le 1\} .$$

At the beginning interval $[t_0, t_e]$ is divided into $n = 10$ equal parts. On each part control function u is approximated by constant function. Choosing different initial values of optimization parameters b_i, $i = \overline{1,10}$ we usually obtain such values optimization

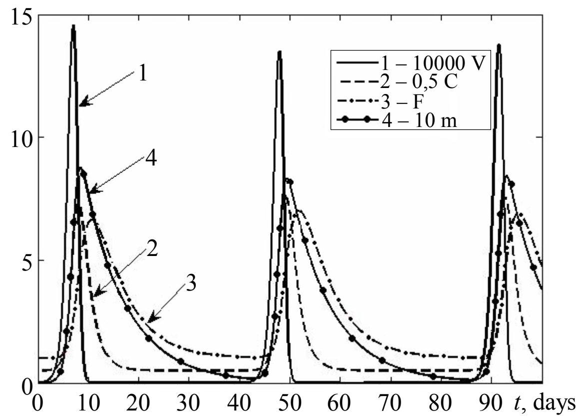

Fig. 2. Variation of V, C, F, m with time
(chronic form, $u(t) = 0$)

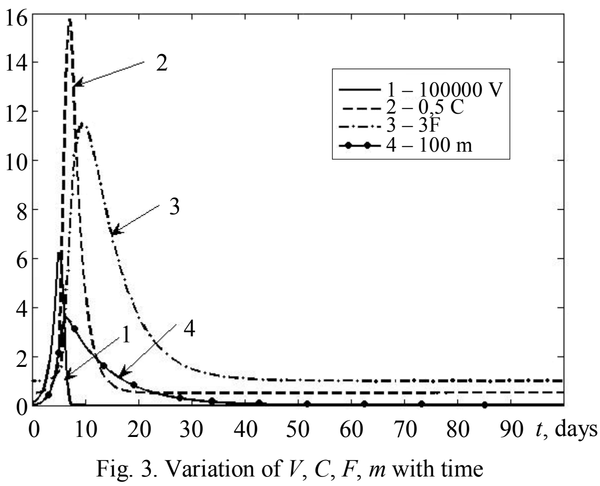

Fig. 3. Variation of V, C, F, m with time
(optimal solution of problem (11))

parameters which lead to the acute form of the disease. As in the previous case of the acute form of the disease we can choose nonzero control function only in interval $[t_a, t_b]$ which includes the first peak of the disease. Therefore the optimization problems (9)-(11) can be formulated.

The results of problems (9)-(11) solution are presented in Table 3, Table 4. Interval [0; 20] is divided into $n = 4$ equal parts. In each part the control function u is approximated by the constant function. In interval [20; 100] the control function $u(t)$ is equal to zero.

Table 3

Initial and optimal values of functionals $\tilde{\varphi}_i$, $i = 1,4,6,7$ (chronic form)

Number of functional, i	Initial value of functional $\tilde{\varphi}_i$	Optimal value of functional $\tilde{\varphi}_i$, problem (9)	Optimal value of functional $\tilde{\varphi}_i$, problem (10)	Optimal value of functional $\tilde{\varphi}_i$, problem (11)
1	$2{,}42\cdot10^{-1}$	$1{,}77\cdot10^{-1}$ (*)	$9{,}58\cdot10^{-1}$	$3{,}79\cdot10^{-1}$ (*)
4	$8{,}77\cdot10^{-1}$	$1{,}55\cdot10^{-2}$	$9{,}58\cdot10^{-2}$	$3{,}57\cdot10^{-2}$
5	—	15,8	8,09 (*)	10,0 (+)
6	40,9	—	—	—
7	$1{,}09\cdot10^{-2}$	$7{,}10\cdot10^{-5}$	$3{,}84\cdot10^{-4}$	$1{,}51\cdot10^{-4}$

Table 4

Optimal values of optimization parameters b_i, $i = \overline{1,4}$ (chronic form)

optimization parameter	Optimal value of b_i, problem (9)	Optimal value of b_i, problem (10)	Optimal value of b_i, problem (11)
b_1	0,354	0,051	0,189
b_2	1,000	0,978	1,000
b_3	0,843	0,900	0,883
b_4	0,208	0,001	0,010

Variation of V, C, F, m with time of the disease process using optimal values of the optimization parameters is presented in Fig. 3. Therefore the chronic form of the disease can be treated by changing temperature.

Conclusions. The obtained results of computer simulation demonstrate the capabilities of the created software environment for solving urgent optimization problems for the processes that are modelled by DDEs. It is necessary to note that usually functionals φ_i, $i = \overline{0,M}$ (in DDEs optimal control problem) are non-unimodal and have deeply curved valley forms. They are very sensitive to small variation of a control function. Therefore to obtain the optimal solution it is necessary to solve repeatedly the optimal control problem choosing different initial values of the control function.

The results presented in this paper for infectious disease processes have in many cases a theoretical character. Working out practical recommendations connected with the optimization of the individual therapy and their introduction into clinical practice requires the joint efforts of mathematicians, immunologists and clinicians.

Availability of a set of parameters g in the mathematical model of the disease leads to a necessity to determine their values (or some part of them) based on clinical and laboratory observed data [1, 5, 7]. This simulation tool enables us to solve the optimization problem (and correct therapy) taking into account the data of clinical and laboratory observation which is obtained during the treatment process [7].

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Оптимізація процесів інфекційних захворювань, які моделюються нелінійними диференціальними рівняннями із запізненням

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У роботі запропоновано числовий підхід до розв'язування задач оптимізації процесів, поведінка яких моделюється нелінійними диференціальними рівняннями із запізненням (ДРЗ) з постійним кроком запізнення. На основі отриманого розв'язку для ДРЗ обчислюються відповідні характеристики процесу, що розглядається. Одна з цих характеристик вибирається за критерій оптимізації, а інші виконують роль обмежень. За керуючі вибрано функції, від яких залежать коефіцієнти ДРЗ. У результаті апроксимації функцій керування кусково-лінійними функціями отримуємо задачі нелінійного математичного програмування. Ефективність створеного програмного забезпечення для розв'язування нелінійних ДРЗ і задач оптимізації систем, поведінка яких моделюється ДРЗ, проілюстровано на прикладі моделі інфекційного захворювання.

Оптимизация процессов инфекционных заболеваний, моделирующихся нелинейными дифференциальными уравнениями с запаздыванием

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В работе предложен численный подход к решению задач оптимизации процессов, поведение которых моделируется нелинейными дифференциальными уравнениями с запаздывающим аргументом (ДУЗ) с постоянным шагом запаздывания. На основе полученного решения для ДУЗ исчисляются соответствующие характеристики рассматриваемого процесса. Одна из этих характеристик выбирается критерием оптимизации, а другие выполняют роль ограничений. В качестве управляющих выбрано функции, от которых зависят коэффициенты ДУЗ. В результате аппроксимации функций управления кусочно-линейными функциями получаем задачи нелинейного математического программирования. Эффективность созданного программного обеспечения для решения нелинейных ДУЗ и задач оптимизации систем, поведение которых моделируется ДУЗ, проиллюстрировано на примере модели инфекционного заболевания.

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