Algorithmic method for modeling the optimal treatment of patients with HIV

Anna P. Presnova
National Research University Higher School of Economics, Tallinskaya street 34, Moscow, Russia
E-mail: apresnova@hse.ru

Abstract. The mathematical model describing the dynamics of HIV in the human body is a nonlinear system of differential equations. This model takes into account the effect of drugs on the body. Thus, it is possible to obtain "optimal" treatment regimens for patients, which cause minimal harm to the body. In the work for constructing suboptimal control of the supply of drugs, the method of "extended linearization" is used, which makes it possible to switch from a nonlinear model to a linear model, but with parameters that depend on the state. To solve the resulting equation Riccati and search for control actions, a method is proposed for the formation of optimization algorithms for nonlinear control systems based on the application of functions of admissible values of control actions.

1. Introduction
The problem of optimal control synthesis for a nonlinear system of differential equations describing some real process is relevant today. Since the theory of control of linear systems is sufficiently developed, various linearization methods are often used to synthesize nonlinear control systems. In this paper, we use the extended linearization method, which allows us to go from the initial nonlinear model to a linear model, but with parameters depending on the state. In the literature, such a representation of the original model is called the SDC representation [1]. Such a transition makes it possible to find the optimal control not by using the partial derivative solution of the Hamilton-Jacobi-Bellman equation, but to proceed to solving a Riccati-type equation with state-dependent parameters. Solving this equation at the pace of system operation is also not an easy task. To solve the resulting equation, an algorithmic method of parametric optimization of the object is proposed. This method is based on the necessary conditions for optimality of the system, which consist in a certain behavior of the Hamiltonian on the optimal trajectory.

The proposed algorithm is applied to a mathematical model of the human immune system in the presence of HIV in the body. The synthesis of suboptimal control, controlling the flow of drugs. The simulation was carried out in the package MATLAB Simulink. The simulation results confirm the correct operation of the algorithm.
2. Nonlinear system and optimal control

Consider a controllable non-linear system described by the differential equation

\[
\frac{d}{dt}x(t) = f(x(t)) + B(x(t))u(t),
\]

\[x(t_0) = x_0,\tag{1}\]

where \(x(t) \in \mathbb{R}^n\) - the state of the system; \(x_0 \in X_0\) - the set of possible initial conditions of the system; \(y(t) \in \mathbb{R}^m, m \leq n\) - system output; \(u(t) \in \mathbb{R}^r\) - control to be found; \(f(x), B(x)\) - real continuous matrix functions of appropriate dimensions.

Introduce the cost functional

\[
J(x(\cdot), u(\cdot)) = \frac{1}{2} \int_{t_0}^{t_f} \{ x^T(t)Qx(t) + u^T(t)Ru(t) \} dt. \tag{2}
\]

In functional (2) a symmetrical matrices \(Q\) and \(R\) are positive definite. Limitations on control actions are taken into account when assigning a positive definite matrix \(R\). The problem consists in construction of an optimal control \(u(t)\) minimizing a functional of (2) on the object (1).

The system (1) is assumed controllable and observable. It is also assumed that the condition \(x = 0\) is the equilibrium point of the system where \(u = 0\) so that \(f(0) = 0\) and \(B(x) \neq 0\).

Suppose that function \(f(x(t))\) - continuous differentiable with respect to \(x \in \Omega\), i.e. \(f(\cdot) \in C^1(\Omega_x)\). In addition, we shall assume that the functions \(f(x(t)), B(x(t))\) such that for any initial conditions \((t_0, x_0) \in \mathbb{R}^+ \times \Omega_x\) only one solution \(x(t, t_0, x_0)\) of (1) is possible.

Optimal control for the initial system, as is known from the theory of analytical construction, is determined by the expression

\[
u(t) = -R^{-1}B^T(x(t)) \left\{ \frac{\partial V(t, x(t))}{\partial x} \right\}^T, \tag{3}\]

where vector \(\left\{ \frac{\partial V(t, x)}{\partial x} \right\}^T\) is a solution of the Hamilton-Jacobi-Bellman equation [2]:

\[
\frac{\partial V(t, x(t))}{\partial t} + \frac{\partial V(t, x(t))}{\partial x} f(x(t)) - \frac{1}{2} \frac{\partial^2 V(t, x(t))}{\partial x^2} B(x(t)) R^{-1} B^T(x(t)) \left\{ \frac{\partial V(t, x(t))}{\partial x} \right\}^T + \frac{1}{2} x^T(t) Q x(t) = 0, \tag{4}\]

where \(V(t, x(t))\) - function, defined as

\[
V(s, x(\cdot)) \triangleq \inf_{u(\cdot) \in U} \left[ \frac{1}{2} \int_s^{t_f} \{ x^T(t)Qx(t) + u^T(t)Ru(t) \} dt \right]. \tag{5}\]

The realization of controls in the form (3) encounters difficulties connected with solving a scalar partial differential equation (4).
3. The method of extended linearization and SDRE
Using the extended linearization method, we will present the original model in the form

\[ \frac{d}{dt} x(t) = A(x(t))x(t) + B(x(t))u(t), \]
\[ x(t_0) = x_0. \]  

(6)

It should be noted that such a presentation is not the only one. The problem of choosing the optimal representation has not been solved yet. To find solutions of the Hamilton-Jacobi-Bellman equation (4), we introduce the relation

\[ \{\partial V(t,x(t))/\partial x\}^T = S(x(t))x(t), \]

(7)

where \( S(x(t)) \) - a positive definite symmetric matrix, allows when searching for optimal controls, to pass from the solution of the Hamilton-Jacobi-Bellman equation in partial derivatives (4) to an equation of the form:

\[ \left[ \frac{d}{dt} S(x(t)) + A^T(x(t))S(x(t)) + S(x(t))A(x(t)) - S(x(t))B(x(t))R^{-1}B^T(x(t))S(x(t)) + Q + \left\{ \left[ \frac{\partial A(x(t))}{\partial x} \right]^T \otimes x(t) + \left[ \frac{\partial B(x(t))}{\partial x} \right]^T \otimes u(t) \right\} S(x(t)) \right] x(t) = 0, \]

(8)

where \( \otimes \) - Kronecker multiplication symbol. The solution of the resulting equation (8) also presents a certain difficulty, therefore, we consider the case with an unlimited transition time.

In this case (8) can be written as algebraic equation of Riccati type with the state dependent coefficient [3]:

\[ A^T(x(t))\hat{S}(x(t)) + \hat{S}(x(t))A(x(t)) - \hat{S}(x(t))B(x(t))R^{-1}B^T(x(t))\hat{S}(x(t)) + Q = 0. \]

(9)

And the control will be written as

\[ u(t) = -R^{-1}B^T(x(t))\hat{S}(x(t))x(t). \]

(10)

Since the control action \( u(t) \) is determined by the expression (10), into which the matrix \( \hat{S}(x) \) enters, which in the general case is not equal to \( S(x) \), the solution of the equation (8), then the control (10) is more correctly called suboptimal. In [4], a theorem is proved that the resulting suboptimal control provides the system (1) local asymptotic stability.

4. The parametric optimization algorithms
In this paper, to solve the resulting equation (9) and synthesize suboptimal controls of a nonlinear object, an algorithmic method for constructing control actions based on the behavior of the Hamiltonian along the optimal trajectory will be proposed.

For this, we consider a controllable object described by a nonlinear equation of a general form

\[ \frac{d}{dt} x(t) = f(x(t), u(t), \eta(t), a(t)), \]
\[ x(t_0) = x_0. \]  

(11)

where \( x \in \mathbb{R}^n, u \in \mathbb{R}^r, \eta \in \mathbb{R}^k \) - vector of object parameters exposed to uncontrolled disturbances, \( a \in \mathbb{R}^p \) - vector of system optimization object parameters. We note that in the general case \( k \geq p \). The parameters of the system selected for parametric optimization can be found both in the object itself and in the regulator.
Let us consider the behavior of the Hamiltonian on the optimal trajectory. Differentiating $H(t, x, u, \lambda)$ in respect of time, taking into account the possibility of transition to an open field of control actions, we obtained:

$$\frac{d}{dt} H(t, x(t), u(t), \lambda(t)) = \frac{\partial H(t, x(t), u(t), \lambda(t))}{\partial t}. \quad (12)$$

The behavior of the Hamiltonian under optimal control changes during a transient process along a completely defined trajectory determined by solving the differential equation (12). This property of the Hamiltonian was used as the basis for the design of algorithms for optimizing the control system.

The necessary conditions for the minimum of the quality functional, expressed in the behavior of the Hamiltonian on the optimal trajectory, are written with the help of a scalar function $\Re(t)$ such as

$$\Re^0(t) = H^0(t) + \varphi(t) = 0, \quad (13)$$

where the scalar function $\varphi(t)$ takes specific values for each problem under consideration and $H^0(t) = H(t, x^0, u^0, \lambda^0) = \varphi(t)$ - is the value of the Hamiltonian at each instant of control time in the absence of parametric disturbances (or when they are completely parried) under optimal control and the corresponding trajectory of the system. It is obvious that, if in $a(t) \neq \eta(t)$, then (13) will not be satisfied, i.e. $\Re(t) = H(t) + \varphi(t) \neq 0$. Let us take the Lyapunov function into consideration

$$V_L(\eta, a) = \frac{1}{2} \{ \Re(t) - \Re^0(t) \}^2 = \frac{1}{2} \{ \Re(t) \}^2. \quad (14)$$

Then for local asymptotic stability, its derivative should be nonpositive:

$$\frac{d}{dt} V_L(\eta, a) = \Re(t) \left\{ \frac{\partial H(t, x(t), u(t), \lambda(t))}{\partial \eta(t)} \frac{d}{dt} \eta(t) + \frac{\partial H(t, x(t), u(t), \lambda(t))}{\partial a(t)} \frac{d}{dt} a(t) \right\} \leq 0, \quad (15)$$

since

$$\frac{\partial H(t, x(t), u(t), \lambda(t))}{\partial t} = \frac{\partial H^0(t, x(t), u(t), \lambda(t))}{\partial t}, \quad \frac{\partial \varphi(t)}{\partial \eta(t)} = 0, \quad \frac{\partial \varphi(t)}{\partial a(t)} = 0. \quad (16)$$

Let the algorithm of parametric optimization have the form

$$\frac{d}{dt} a(t) = - \left\{ \frac{\partial H(t, x(t), u(t), \lambda(t))}{\partial a(t)} \right\}^T \Re(t), \quad (17)$$

$$a(t_0) = a_0.$$

Consider another parametric optimization algorithm, in the form

$$\frac{d}{dt} a(t) = \Im(t) \Re(t), \quad (18)$$

where the function $\Im(t)$ determines the direction and rate of change of the optimization parameters. Assigning the Lyapunov function in the same form as in the previous case, condition (15) is obtained as

$$\Re(t) \frac{\partial H(t, x(t), u(t), \lambda(t))}{\partial \eta(t)} \frac{d}{dt} \eta(t) - \Re^2(t) \frac{\partial H(t, x(t), u(t), \lambda(t))}{\partial a(t)} \Im(t) \leq 0. \quad (19)$$

Then the algorithm (17) takes the form

$$\frac{d}{dt} a(t) = - \left\{ \frac{\partial H(t, x(t), u(t), \lambda(t))}{\partial a(t)} \right\}^T \Re^2(t), \quad (20)$$

$$a(t_0) = a_0.$$

Consider another parametric optimization algorithm, in the form
These algorithms are assigned in this form is not accidental, with the same values, they have unequal efficiency. In the case of a function $|\Re(t)| < 1$, the restructuring of the parameters occurs faster with the algorithm (17). If the values of the function $|\Re(t)| > 1$, then the speed of parameter adjustment is higher when using the algorithm (20).

5. Mathematical model of the human immune system with HIV

The model consists of five differential equations [5]:

$$\frac{d}{dt}i(t) = \lambda - di(t) - \beta(1 - \eta u)i(t)y(t),$$

$$\frac{d}{dt}y(t) = \beta(1 - \eta u)i(t)y(t) - ay(t) - p_1z_1(t)y(t) - p_2z_2(t)y(t),$$

$$\frac{d}{dt}z_1(t) = c_1z_1(t)y(t) - b_1z_1(t),$$

$$\frac{d}{dt}w(t) = c_2i(t)y(t)w(t) - c_2qy(t)w(t) - b_2w(t),$$

$$\frac{d}{dt}z_2(t) = c_2qy(t)w(t) - hz_2(t),$$

where $i$ - concentration of uninfected cells of the immune system, T-helpers; $\lambda$ - the production rate of T-helpers in the body; $d$ - rate of natural death of T-helpers. When a virus enters the bloodstream, T-helper cells become infected at a rate $\beta$ and become infected cells ($y$), that is the HIV. The infected cells naturally die at the rate $a$, in addition T-killers ($z_1$) kill them at the rate $p_1$, and immunoglobulins ($z_2$) kill the infected cells at the rate $p_2$. B-lymphocytes ($w$) are activated in the body at the speed $c_2$, and at the speed $q$ they turn into immunoglobulins. The maximum effectiveness of drugs is expressed by the coefficient $\eta$, $u$ - the dose of the drug administered, that is, our intervention. The values of the parameters are taken from [6].

It is for this model we shall synthesize the suboptimal administration of drug delivery, found by means of the algorithmic method. To do this, the initial nonlinear model (21) using the method of ”extended linearization” will be represented as (6). Here the matrix has an ambiguous representation, as mentioned earlier.

To find a suboptimal control in the form of (10), it is necessary to find the matrix $S(x(t))$, which is a solution of the Riccati equation with state-dependent parameters (9), which is not an easy task. To find the matrix $S(x(t))$ we use the algorithmic method. Let us present the matrix $S(x(t))$ in the form

$$S(x) = S_0 + s(t),$$

where the matrix $S_0$ is found from the solution of the Riccati equation with constant parameters (at $x(t_0) = x_0$). In this problem $H \{x^0, u^0, S(x^0)x^0\} = 0$ - is the behavior of the Hamiltonian on the optimal trajectory. In accordance with the above method of forming the parametric optimization algorithms (17) and (20), where $\Re(t) = H \{x^0, u^0, S(x^0)x^0\} = H \{x, u, [S_0 + s(t)] x\}$, the algorithms takes the form

$$\frac{d}{dt}s(t) = -\left\{\frac{\partial H \{x, u, [S_0 + s] x\}}{\partial s(t)}\right\}^T H \{x, u, [S_0 + s] x\}, \text{ if } |H| \leq 1;$$

$$\frac{d}{dt}s(t) = -\left\{\frac{\partial H \{x, u, [S_0 + s] x\}}{\partial s(t)}\right\}^T H^2 \{x, u, [S_0 + s] x\}(t), \text{ if } |H| > 1;$$

$$s(t_0) = 0.$$
6. Computer simulation and results

Computer simulation of the synthesized control actions was carried out in the MATLAB Simulink package. For example, a very weak patient with an HI virus is considered. The simulation was carried out for a given initial state in two modes: in the treatment synthesized by the algorithmic method, and in the absence of any treatment, that is, when \( u = 0 \). The obtained simulation results for the chosen mathematical model of the immune system of a person with HIV demonstrate the success of the constructed control using the algorithmic method.

![Figure 1](image1.png)  
**Figure 1.** The concentration of healthy cells of the immune system in the presence of HIV.

![Figure 2](image2.png)  
**Figure 2.** The concentration of cells of the immune system infected with HIV in the human body.

![Figure 3](image3.png)  
**Figure 3.** Hamiltonian.

![Figure 4](image4.png)  
**Figure 4.** Matrix \( s(t) \).

References

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