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Applications of Control Theory in Cancer Research

A. Asachenkov
N. Grigorenko

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IIASA International Institute for Applied Systems Analysis □ A-2361 Laxenburg □ Austria
Telephone: +43 2236 715210 □ Telex: 079 137 iiasa a □ Telefax: +43 2236 71313

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Foreword

This paper deals with some optimal control problems in cancer research. The respective problems arise from applied motivations that come from biological and medical issues. The influence of treatment on the disease history, the performance criterion, the statement of the optimal control problems and a solution of the synthesis problem are discussed.

Applications of Control Theory in Cancer Research.

A.Asachenkov

International Institute for Applied Systems Analysis

Laxenburg, Austria

N.Grigorenko

Moscow State University

Moscow, Russia

Even though much progress has occurred in cancer research, many problems are still unresolved. The absence of specific identifiable differences between normal and malignant cells is a major barrier that has limited the development of specific anticancer therapy. Treatment has had to rely on spatial separation of tumor and critical normal tissues (surgery or radiotherapy), or on minor and normal tissues to systemic treatments such as chemotherapy. Thus almost all types of cancer treatments cause significant damage to normal tissue. There is little information on pharmacokinetics and other factors associated with effective concentrations of each drug at receptor sites; anticancer drugs have narrow therapeutic indices, are unstable, and have ill-defined metabolism.

1. Introduction

Systematic treatment with cytotoxic drugs is often the only treatment that may influence all sites of metastatic disease. At tolerated doses, such treatment can be highly effective for certain types of cancer (lymphomas and testicular cancer), but it is rarely effective for many of the common types of solid tumors (colo-rectal or lung carcinoma). A major limitation to the success of drug treatment is the presence in the tumor of drug-resistent cells which convey either initial resistance to treatment, or subsequent resistance after the tumor has initially responded.

Alternative approaches to cancer treatment include the use of hormones, which may be effective in inducing remission, but not cure, some cancers that arise in hormone-sensitive tissues such as breast and prostate. Hyperthermia is being investigated as an alternative or auxiliary treatment which can be combined with ionizing radiation or chemotherapy, but it remains unclear whether heat can provide selective toxicity to tumor cells.

Various approaches to immunotherapy have been tried clinically but classical approaches involving attempted immunization have met with minimal success. The development of monoclonal antibodies and of a number of agents which can stimulate specific components of the immune response (interferons, interleukins, tumor necrosis factor) has rekindled hopes for specific killing of tumor cells via immune-mediated effects.

In this article we plan to discuss some aspects of the optimal management problems in cancer research. According to available information two classes of mathematical models

can be considered. First is a so-called tumor growth model, then the tumor volume or the number of tumor cells can be calculated by means of direct measurements or by using specific "tumor markers". The second one there are no sufficiently specific "tumor markers". In such cases to study the tumor growth process we may use clinically measured laboratory indices. Good examples are given by Rescigno and DeLisi, Grossman and Berke, Lefever and Garay, DeBoer and Hogeweg, Asachenkov, Mohler and Lee.

Consider the simple example. Let z(t) be the number of tumor cells, $z(t) > 0$ for $t \geq 0$, and $t=0$ be the instant of surgery to remove the solid tumor. Formally, the continuous tumor growth model has the following form

$$\frac{dz}{dt} = f(z), \qquad z(t_0) = z_0 > 0 \tag{1}$$

where $z(t) \in R_+$, and f(z) is a rule a know nonlinear function. If $f(z) = \lambda z \ln(z_{max}/z)$, where z_{max} is the largest size of the tumor and λ is a constant we have the so-called Gompertz growth equation

$$\frac{dz}{dt} = \lambda z \, ln(z_{max}/z). \tag{2}$$

An analytical solution of this equation can be obtained by using the transformation $y = \ln(z/z_{max})$, then

$$\frac{dy}{dt} = - \lambda y. \tag{3}$$

The anticancer drugs influence tumor growth. The real problem is to describe the therapy (control) in mathematical terms. If we suggest that the action of drug proportional to the population of tumor cells in the form v(u)z, where v(u) is a known function. We can write the perturbed tumor growth model

$$\frac{dz}{dt} = \lambda z \ ln(z_{max}/z) - v(u)z, \qquad z(0) = z_0 \tag{4}$$

Unfortunately, we have no recommendation to decide on an appropriate form for v(u). For our example, the following expression looks reasonable (Swan, 1984)

$$v(r) = \frac{k_1 r}{k_2 + r}, \qquad k_1, k_2 = const>0 \tag{5}$$

Now, lets $\tau=\lambda t$, $u=r/k_2$, $p=k_1/\lambda$ then

$$\frac{dy}{d\tau} = - y - \frac{pu}{1 + u}, \qquad y(0)= - c$$
$$c= ln(z_{max}/z_0), \qquad p>c. \tag{6}$$

Another problem consists in the selection of suitable performance criteria. One of the simplest way is a following. It is known, that anticancer drugs are toxic. In the absence of additional information, let us consider the following measure

$$J = \int_0^T u(t)dt. \tag{7}$$

where u(t) is a nondimentional input of drug and t is a nondimensional time.

Now using the Pontryagin Maximum Principle we can write an analytical solution for a control variable

$$u(\tau) = [\ 1 - (c/p)^{1/2}\ ]^{-1}\exp(\tau/2) - 1 \qquad (8)$$

and

$$y(\tau) = - p\ \{\ 1 - [\ 1 - (c/p)^{1/2}\ ]\exp(-\tau/2)\ \}^2 \qquad (9)$$

Here y leads to (-p) for large time. This means that even with unbounded control a plateau level for y is eventually reached beyond which the number of cancer cells cannot be reduced. The problem becomes more difficult when we deal with more sophisticated models. Some of the preliminary results are presented in the next Sections.

2. The controlled dynamic system

Let us consider the dynamics of observed indices from the patients after surgery. Let $t=0$ be the instant of surgery. Denote $x(t)\epsilon R^n$ vector measured in clinic indices. Development of disease leads to deviations of these indices from the values corresponding to the healthy organism. Let the dynamics of the clinically measured indices, on the average, be described by the equation

$$\frac{dx(t)}{dt} = f(x;p^*)\ , \qquad x(0)=x_0\geq 0\ , \qquad t\geq 0$$
$$x\in\mathbb{R}^n\ , \qquad p^*\in\mathbb{R}^l\ . \qquad (10)$$

where p^* is parameter.

In the mathematical modelling, two approaches can be used to include a control in the model parameters. In the stochastic scheme we suppose that the individual trajectories of these indices have presumably stochastic character, and for computer simulation ODE with random perturbations of parameters can be used (Asachenkov, Marchuk, Mohler, Zuev).

$$\begin{aligned} \frac{d}{dt}x_t^\varepsilon &= f(x_t^\varepsilon, p^* + \xi_{t/\varepsilon}), \\ x_0^\varepsilon &= x_0, \qquad t\in[0,T] \end{aligned} \tag{11}$$

Here x_t^ε is a perturbed solution, $\varepsilon > 0$ is a small parameter, ξ_t is a stochastic process such that $E\xi_t=0$ and $\mathrm{cov}(\xi_t,\xi_{t+\tau}) \to 0$ as $\tau \to \infty$. These trajectories can be considered as a result of small perturbations of dynamic system. The perturbed motion described by this model is the fast random fluctuation along the reference trajectory $x_t(p^*)$. Let $Y_t^\varepsilon = x_t^\varepsilon - x_t(p^*)$ be a deviation between the perturbed motion and reference trajectory. Then, the process Y_t^ε is approximated by the lineal stochastic differential

$$dY_t = a(t)Y_t dt + b(t)dw_t, \tag{12}$$

where w_t is a Gaussian stochastic process with independent increments (Zuev, 1988).

The effect of drug action is manifested by the dynamics of the measurable indices and survival function. There are two possibilities to incorporate the control variables in the model:

1. The action of an anticancer drugs is proportional to the population of the cancer cells;

2. Drug administration changes the parameters of the model.

The problem is to construct the function a(t,u) and b(t,u) on the basis of available information. Let A_0 - be the group of patients with surgery only, A_1 - be the group of patients with surgery and treatment (chemotherapy and etc).

The experimental data from the patients with stomach cancer show that the character of the x(.) dynamics in the groups A_0 and A_1 are similar and , consequently, can be described by the equation of the same structure (Asachenkov et al. 1990). By taking into consideration this fact we can formulate the following

Hypothesis. *The dynamics of measurable variables in the groups of* A_0 *and* A_1 *are described by the same equation with the parameters* p^* *and* p_1, $p^* \neq p_1$, *respectively. The difference between the coefficients is determined by the cancer therapy (control).*

$$p_1 = p^* + \beta u(t), \qquad u(t) \in U, \qquad \beta = const. \tag{13}$$

Under the hypothesis the perturbed controlled model is

$$\begin{aligned} \frac{d}{dt} x_t^\varepsilon(u) &= f(x_t^\varepsilon, p^* + \beta u(t) + \xi_{t\varepsilon}), \\ x_0^\varepsilon(u) &= x_0(p^*), \qquad t \in [0,T] \end{aligned} \tag{14}$$

and the model for the deviations $Z_t = x_t^\varepsilon - x_t(u,p^*)$ can be approximated by the following SDE

$$\begin{aligned} dZ_t(u) &= a(t,u)Z_t(u)dt + b(t,u)dw_t, \\ Z_0(u) &= 0. \end{aligned} \tag{15}$$

Here $EZ_t=0$ for all $\forall_{t\geq 0}=0$ and $x_t(u,p^*)$ is a solution of

$$\begin{aligned} \frac{d}{dt}x_t(u,p^*) &= f(x_t, p^* + \beta u(t)), \\ x_0(u,p^*) &= x_0(p^*), \qquad t\in[0,T] \end{aligned} \tag{16}$$

Another scheme is based on the idea that the parameters of the model are connected by means of some common factor (Asachenkov, Pogozchev, Zuev, 1992). This means that if p^* is a known vector such that the model

$$\begin{aligned} &\frac{d}{dt}x_t = f(x_t,p^*), \qquad x_0 = c, \quad t\in[0,T], \\ &x_t\in\mathbb{R}^n, \qquad p^*\in\mathbb{R}^l \end{aligned} \tag{17}$$

describes the average dynamics, then the individual dynamics for the k-th patient can be described in the form:

$$\begin{aligned} &\frac{d}{dt}x_t^k = f(x_t^k,p^*+\beta u(t),HL^k), \qquad x_0 = c^k, \quad t\in[0,T], \\ &x_t^k\in\mathbb{R}^n, \qquad p^*\in\mathbb{R}^l, \qquad HL\in\mathbb{R} \end{aligned} \tag{18}$$

This means that for the individual evaluation of the model parameters we have to estimate only one parameter HL which may be done in the beginning of the disease treatment and then to use the model (18) for the solution of the optimal drug administration problem.

In the deterministic case we assume that the unsertanty $\xi(t)$ is a measurable by Lebesque function from the compact set Ξ and the model equation can be written in the form

$$\frac{dx}{dt} = f(x,p^*+\beta u(t)+\xi(t)), \quad x(0) = x_0, \quad t\in[0,T], \tag{19}$$

where u is a control variable from the appropriate compact set. This type of controled model will study in Section 4.

3. A performance criterion.

In medicine the following scalar cost functional is sometimes used

$$J(u,\xi) = q(x(T)) + \int_0^T R(x,u,\xi)\, dt\ , \tag{20}$$

where q(z(T)) is a function of the state variable at the end of treatment and the second term estimates the cumulative drug toxicity over the time period [0,T]. The optimization problem is to determine the control (administration of drugs) so as to minimize the maximum uncertainty for this performance index.

Consider the model (19) without of $\xi(t)$. Let $y_r(t)$ be a known function. This function prescribe the "desirable" time course for the measured variable and reflects the experience of the investigator. Define $e(t)=x(t)-y_r(t)$, where e(t) is the deviation between the model-derived value x(t) and its desired level. It looks reasonable to use a drug in such a manner, that the measurable variables follows the curve given by $y_r(t)$ with the minimal toxicity

effect

$$J(u) = \int_0^T [\, e^T(t)Q(t)e(t) + u^T(t)Ru(t) \,]dt, \quad u \in U, \tag{21}$$

where Q,R are weighing matrices.

But the function $y_r(t)$, as a rule, is carried out through examination by experts. Therefore, it contains some elements of subjectivity. Is it possible to choose this function using only objective information? Basis on our experience, the answer is "yes". It may be a reference trajectory which describes the average dynamics in the group of patients with "favorable clinical history". Now, it looks reasonable to consider the following cost function

$$J(T) = E\{ \int_0^T Y_t^T Q Y_t + u^T R u \, dt \} \to \min_u \tag{22}$$

Here $Y_t(u) = x_t^{\varepsilon}(u) - x_t(p^*)$ and one of the reason for the appeal of the cost function in the form (22) is the following

Observation. According to (Asachenkov, 1990) the variance of deviations of immunological indices for three groups of patients with stomach cancer differing by the pattern of disease. It is important to note that the variance of deviations of indices from the reference trajectories is *inversely proportional* to the life duration of patients

$$\sigma_1^2 > \sigma_2^2 > \sigma_3^2. \tag{23}$$

The quadratic form (22) represents increased risk for significant deviations from a reference trajectory. It means that to minimize the pathological pressure upon the organism caused by the disease (tumor growth) is equivalent to maximization of the life span after beginning of treatment, and the expression (22) could be considered as a good candidate for the cost function.

4. Statement of the problem.

A commonly accepted criterion of recovery in oncology is a 5-year period in the life of patients from the beginning of his treatment. Because after this, the pattern of the fall in the number of oncological patients in a group of the same age is determined by the magnitude of the natural mortality factor. This means that we can study the optimal treatment problem on the finite interval only.

Let $y(t)>0$, a scalar, denote the state of the system at time t, with $y(T_0)=y_0>0$, u(t) is measurable by Lebesgue function from the compact set [0,1] and its dynamical equation is

$$\begin{gathered} \frac{d}{dt}y = -2(\lambda + \beta u(t))y + (\sigma_1 + \sigma_2 u(t))^2 x^2(t), \\ y,\ u\in\mathbb{R}^1,\quad y(T_0) = y_0\ ,\quad t\in[\ T_0,T\ ],\quad u(t)\in[\ 0,1\ ], \\ x(t) = x_0\exp(-\lambda(T - T_0)), \end{gathered} \tag{24}$$

where u(t) is a control function to be chosen so that one minimizes the cost functional

$$J = \int_{T_0}^{T} [Qy(t) + Ru(t)]dt \to \min_{u} \tag{25}$$

Here x_0, Q, R, T, λ, β, σ_1, σ_2 are positive constants.

The motivation for this type of control problem comes from the study of oncological patients after radical surgery to remove the solid tumor (Asachenkov, 1990).

5. Solution of the synthesis problem.

To solve this control problem we can use the maximum principle of Pontryagin. Denote ψ conjugate variable and introduce Pontryagin's function for the problem (24)-(25)

$$H(t,y,\psi,u) = -(Qy + Ru) + \psi[-2(\lambda + \beta u)y + (\sigma_1 + \sigma_2 u)^2 x^2]. \tag{26}$$

The adjoint equation has a form

$$\frac{d}{dt}\psi = 2(\lambda + \beta u)\psi + Q \tag{27}$$

and the condition of transversality is $\psi(T)=0$.

According to Pontryagin's principle, the extremum control $u^*(t,y,\psi)$ satisfies the conditions

$$for\ \psi < 0$$

$$u^*(t,y,\psi) = \begin{cases} \dfrac{R}{2\sigma_2^2 x^2 \psi} + \dfrac{\beta}{\sigma_2^2 x^2} y - \dfrac{\sigma_1}{\sigma_2} & for\ 0 \le \mu(y,\psi,t) \le 1 \\ 0 & for\ \mu(y,\psi,t) < 0 \\ 1 & for\ \mu(y,\psi,t) > 1 \end{cases} \tag{28}$$

where

$$\mu(y,\psi,t) = \frac{R}{2\sigma_2^2 x^2 \psi} + \frac{\beta}{\sigma_2^2 x^2} y - \frac{\sigma_1}{\sigma_2} \tag{29}$$

$$\begin{aligned} for\ \psi &= 0 \\ u^*(t,y,\psi) &= 0 \end{aligned} \tag{30}$$

$$for\ \psi > 0$$

$$u^*(t,y,\psi) = \begin{cases} 1 & for\ \mu(y,\psi,t) < 0.5 \\ 0 & for\ \mu(y,\psi,t) > 0.5 \\ 0\ or\ 1 & for\ \mu(y,\psi,t) = 0.5 \end{cases} \tag{31}$$

Thus we must study a boundary-value problem (24), (27), with $u=u^*(t,y,\psi)$ (28)-(31) in the rite side to compute the optimal solution.

Statement 1. For the system (27), the terminal condition $\psi(T)=0$ satisfies an admissible control only for the initial values $\psi(T_0)$ from the interval

$$-\frac{Q}{2\lambda} < \psi(T_0) \le 0, \quad T_0 \in [0,T]. \tag{32}$$

By this means the cases (30), (31) can be omitted and we concentrate our attention on the problem (24), (27) and (28). Introducing new variables

$$\begin{aligned} \chi &= y\exp(2\lambda t), \\ \eta &= \psi\exp(-2\lambda t) \end{aligned} \tag{33}$$

and rewrite our problem in the form

$$\begin{aligned} &\frac{d}{dt}\chi = -2\beta u^*\chi + (\sigma_3 + \sigma_4 u^*)^2, \quad \chi(T_0) = y_0\exp(2\lambda T_0), \\ &\frac{d}{dt}\eta = 2\beta u^*\eta + Q\exp(-2\lambda t), \qquad \eta(T) = 0, \\ &\qquad u^*(\chi,\eta,t) = \nu(\chi,\eta) \quad \textit{if} \quad 0 \le \nu(\chi,\eta) \le 1 \\ &\qquad u^*(\chi,\eta,t) = 1 \qquad \textit{if} \quad \nu(\chi,\eta) > 1 \\ &\qquad u^*(\chi,\eta,t) = 0 \qquad \textit{if} \quad \nu(\chi,\eta) < 0 \end{aligned} \tag{34}$$

Here

$$\begin{aligned} \nu(\chi,\eta) &= \frac{R}{2\sigma_4^2\eta} + \frac{\beta}{\sigma_4^2}\chi - \frac{\sigma_3}{\sigma_4}, \\ \sigma_3 &= \sigma_1 x_0\exp(\lambda T_0), \\ \sigma_4 &= \sigma_2 x_0\exp(\lambda T_0). \end{aligned} \tag{35}$$

For u=0 the system (34) has a form

$$\begin{aligned} \frac{d}{dt}\chi &= \sigma_3^2, \\ \frac{d}{dt}\eta &= Q\exp(-2\lambda t), \quad \eta(T)=0. \end{aligned} \tag{36}$$

Then, we have the following:

Statement 2. The solution of the system (24) on the interval [0,T] satisfies the initial condition $\eta(T)=0$ only for

$$\frac{-Q(1-\exp(-2\lambda T))}{2\lambda} \le \eta(0) \le 0. \tag{37}$$

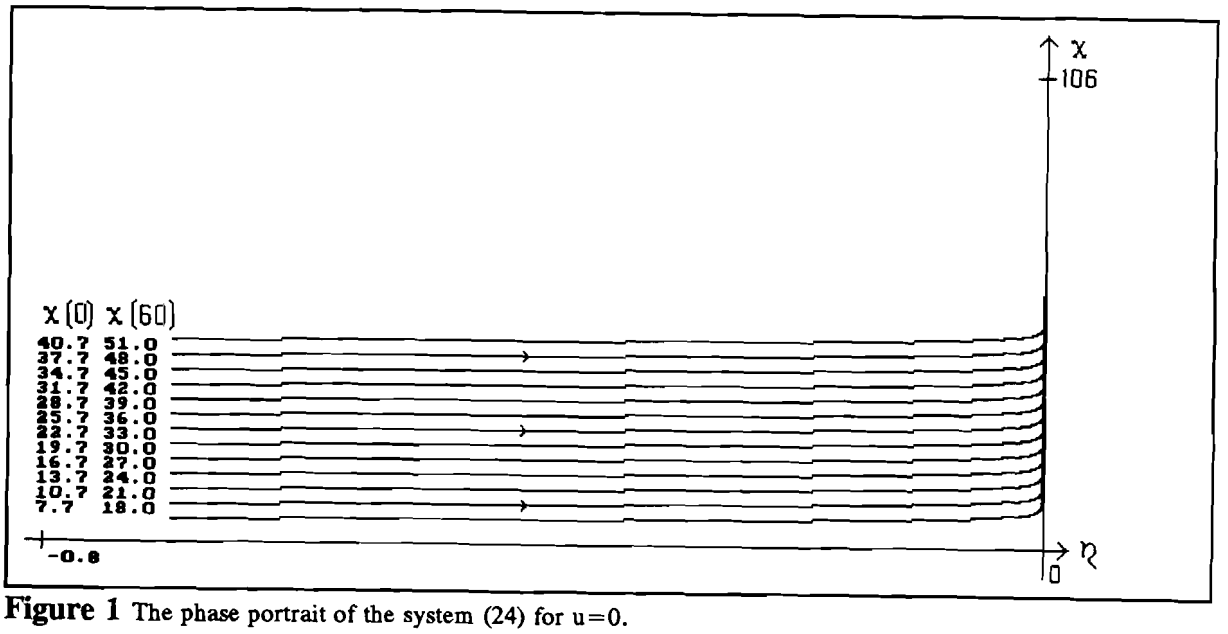

Figure 1 The phase portrait of the system (24) for u=0.

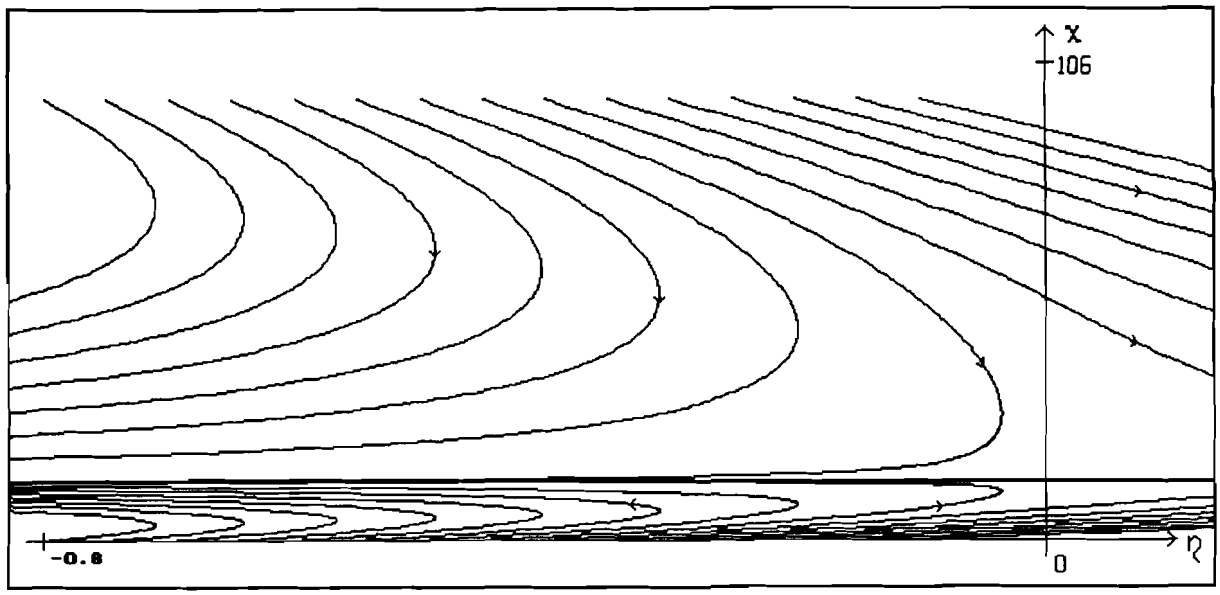

Figure 2 The phase portrait of the system for u=1.

The following conditions hold for the trajectories $\chi(\eta)$: $\chi_\eta' > 0$ for all $\eta < 0$, $\chi_\eta'' > 0$ if $-Q/2\lambda < \eta < 0$ and $\chi_\eta'' < 0$ if $\eta < -Q/2\lambda$. The phase portrait of the system (36) is presented in Fig. 1.

Consider the system (24) for u=1. One is also non-stationary and has a form

$$\begin{aligned} \frac{d}{dt}\chi &= -2\beta\chi + (\sigma_3 + \sigma_4)^2, \quad \chi(T_0) = y_0\exp(2\lambda T_0), \\ \frac{d}{dt}\eta &= 2\beta\eta + Q\exp(-2\lambda t). \end{aligned} \tag{38}$$

The phase portrait of the one is presented in Fig. 2.

Now we study the system (24) for $u=\nu(\chi,\eta)$. We have

$$\frac{d}{dt}\chi = \frac{R^2}{4\sigma_4^2\eta^2} - \frac{\beta^2}{\sigma_4^2}\chi^2 + \frac{2\beta\sigma_3}{\sigma_4}\chi,$$
$$\frac{d}{dt}\eta = \frac{2\beta^2\eta\chi}{\sigma_4^2} - \frac{2\beta\sigma_3\eta}{\sigma_4} + Q\exp(-2\lambda t) + \frac{R\beta}{\sigma_4^2}, \tag{39}$$

in the domain $0 \le \nu(\chi,\eta) \le 1$

$$-\frac{R}{2\beta\eta} + \frac{\sigma_3\sigma_4}{\beta} \le \chi \le -\frac{R}{2\beta\eta} + \frac{(\sigma_3 + \sigma_4)\sigma_4}{\beta}. \tag{40}$$

To study the system (24) introduce four line constants by:

$$\Gamma = \left\{ (\chi,\eta):\ \chi = -\left[\frac{Q\sigma_4^2\exp(-2\lambda t)}{2\beta^2} + \frac{R}{2\beta}\right]\frac{1}{\eta} + \frac{\sigma_3\sigma_4}{\beta},\quad \eta<0 \right\}, \tag{41}$$

This is a set of points for which $\eta_t' = 0$.

$$\Pi = \left\{ (\chi,\eta):\ \chi = \frac{1}{\beta}\left[\sigma_3\sigma_4 + \sqrt{\sigma_3^2\sigma_4^2 + \frac{R^2}{4\eta^2}}\right],\quad \eta<0 \right\}, \tag{42}$$

Which is a set of points for which $\chi_t' = 0$.

$$H = \left\{ (\chi,\eta):\ \chi = -\frac{R}{2\beta}\frac{1}{\eta} + \frac{\sigma_3\sigma_4}{\beta},\quad \eta<0 \right\}, \tag{43}$$

Which is a lower bound of the domain (40).

$$B = \left\{ (\chi,\eta):\ \chi = -\frac{R}{2\beta}\frac{1}{\eta} + \frac{(\sigma_3 + \sigma_4)\sigma_4}{\beta},\quad \eta<0 \right\}, \tag{44}$$

Which is a upper bound for the (40). The lines Π, Γ, B are situated above the one H in the plane (η,χ). The abscissa of intersection point for Π and B is

$$\eta = -\frac{R}{(\sigma_3^2 - \sigma_4^2)}, \tag{45}$$

One of the intersection point for Γ and B is

$$\eta = -\frac{Q\exp(-2\lambda t)}{2\beta}. \tag{46}$$

Let C be a point of intersection for Π and Γ. It is a moving saddle point (Bylov et al, 1966). The form of separatries are given in Fig. 3. The abscissa of the point C is

$$\eta = -\frac{1}{2\sigma_3\exp(2\lambda t)}\sqrt{\frac{Q^2\sigma_4^2}{\beta^2} + \frac{2Q\exp(2\lambda t)}{\beta}}. \tag{47}$$

By virtue of the fact that the system (24) is non-stationary, singular point C is a saddle point and moving from the left to the right. If $Q/2\beta > R/(\sigma_3^2+\sigma_4^2)$ then C is outside of the domain (40) for $0<t\le\ln(Q(\sigma_3^2-\sigma_4^2)/2\beta R)/2\lambda$. Associated phase trajectories are given in Fig.4. For $t>\ln(Q(\sigma_3^2-\sigma_4^2)/2\beta R)/2\lambda$ the point C moving inside one. If $Q/2\beta < R/(\sigma_3^2+\sigma_4^2)$ then C is inside of the domain (40) for $t>0$ and the associated phase trajectories are given in Fig. 3.

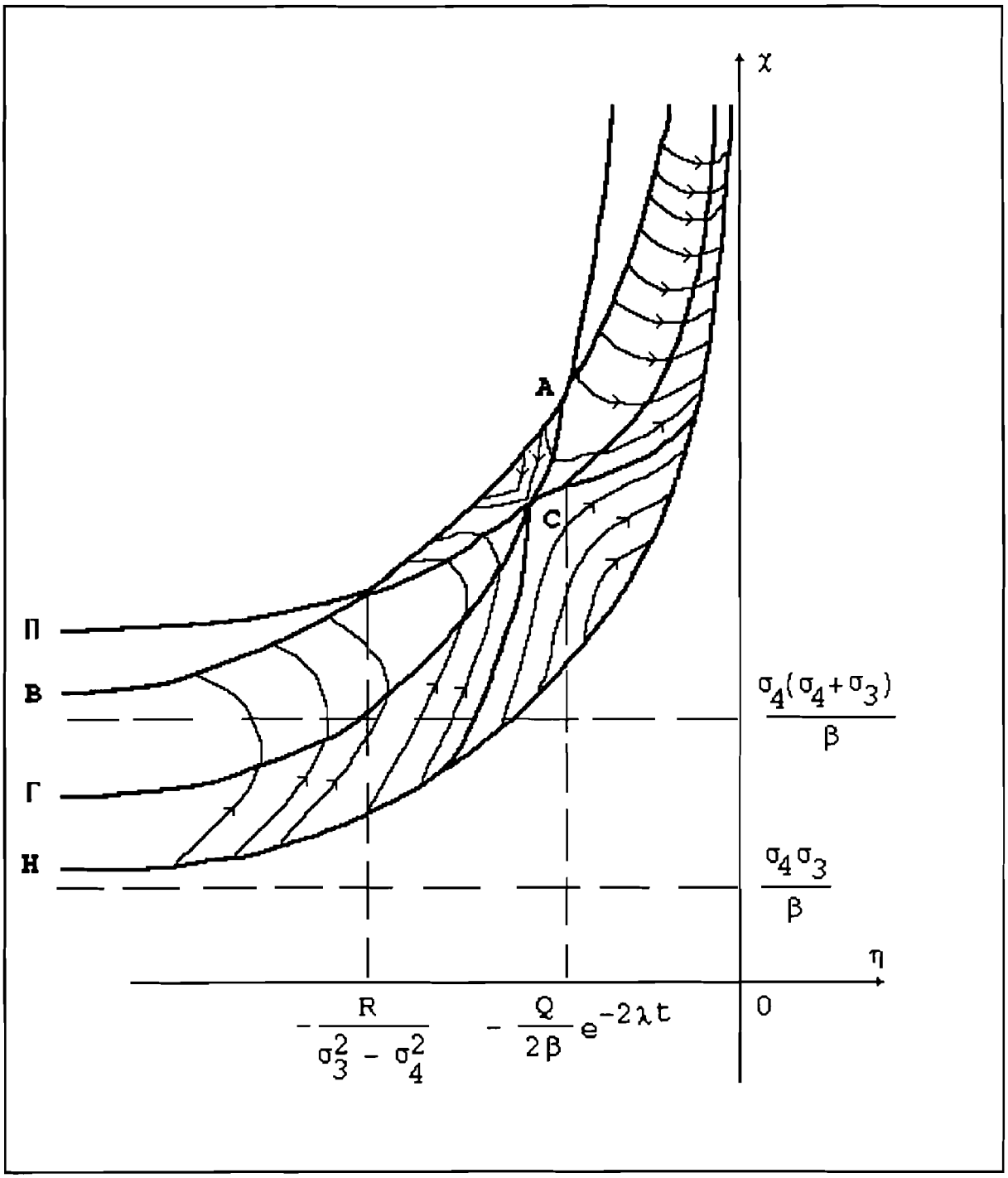

Figure 3 The form of separatries and phase trajectories.

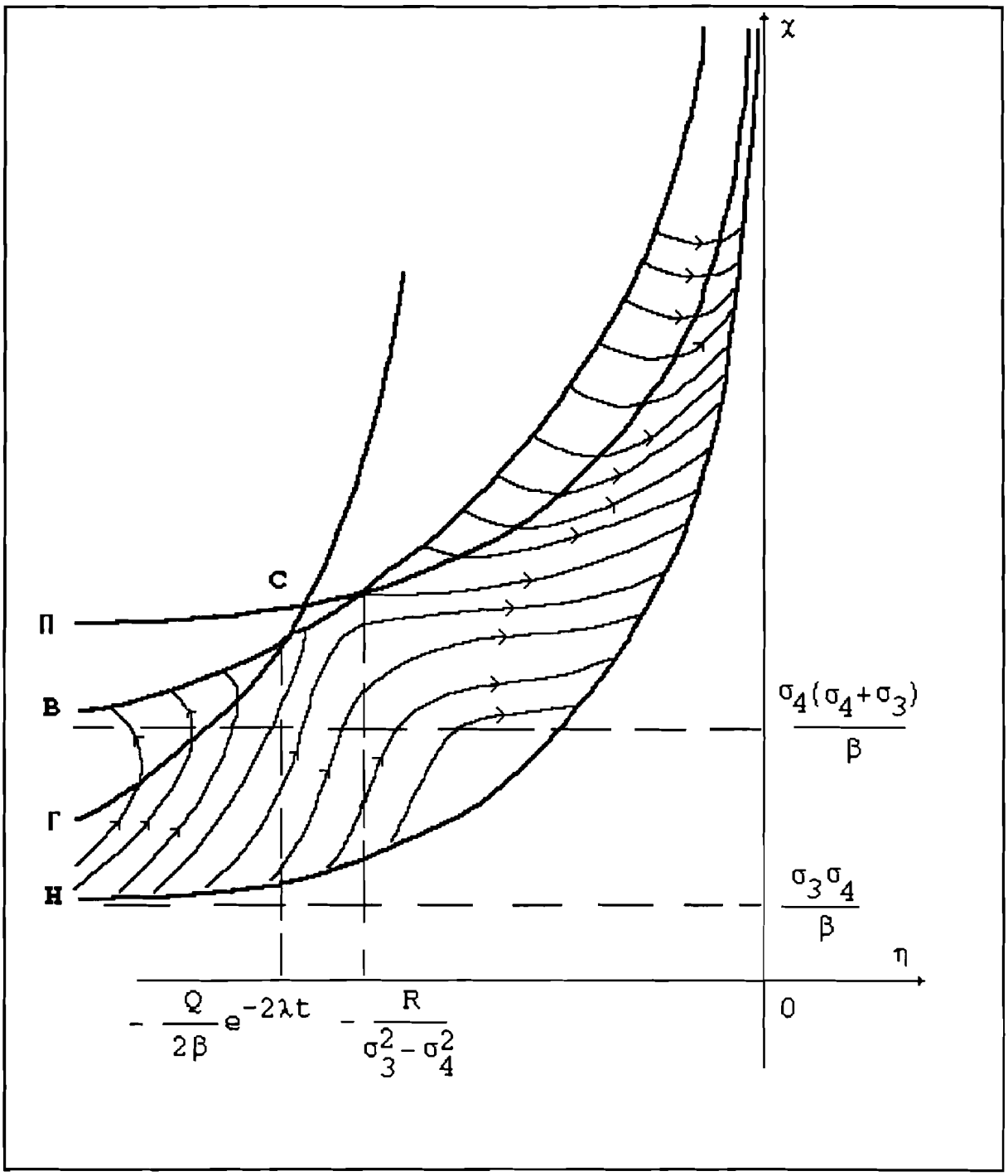

Figure 4 The form of separatries and phase trajectories.

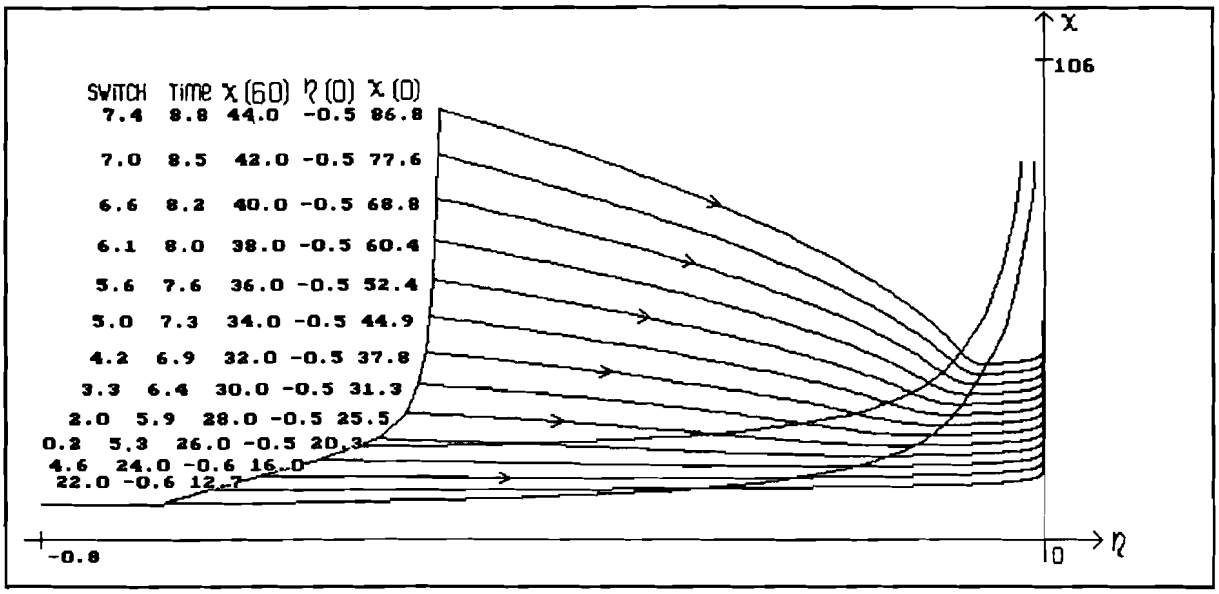

Figure 5 The solution of the synthesis problem (24), (25).

Now consider the problem of synthesis. The conditions of Filipov theorem (Warga) are realized for the extremum problem (24)-(25). The region of the fase space for which the controllability problem on the terminal set is solvable, is field with the trajectories which satisfy to maximum principle. These trajectories do not cross. There are no singular surfaces in the problem (24)-(25). Therefor the extremal trajectories are optimal trajectories. In this case the lines B and H are switching ones. The control is $u=1$ above the line B, $u=\nu(\chi,\eta)$ between B and H, and $u=0$ be low the line H. In Fig. 5 the solution of the synthesis problem are given. Next characteristics are interesting for the practice realization.

Let T_3 be a time of transfer of the system, using $u=0$, from the initial state on the line H at $t=T-T_3$ to the state $\chi(T)$, $\eta(T)=0$ at $t=T$. We can calculate T_3, using (36), (40) and the definition of T_3, by means of the transcendental equation

$$Q\beta\chi(T) - Q\beta\sigma_3^2 T_3 = Q\sigma_3\sigma_4 + \frac{R\lambda\exp(2\lambda T)}{\exp(2\lambda T_3) - 1}. \tag{48}$$

Statement 3. A solution of the equation (48) for T_3 exists

$$T_3^* = \frac{1}{\lambda}\ln\left\{\frac{1}{2\sqrt{A}} + \sqrt{\frac{1}{4A} + 1}\right\}, \qquad A = \frac{\sigma_3^2\beta Q}{2R\lambda^2\exp(2\lambda T)}. \tag{49}$$

This takes place, if the following inequality holds

$$B > 2, \quad T > -\frac{1}{2\lambda}\ln\left\{1 - \frac{2}{B}\right\}, \qquad B = \frac{2\sigma_3}{\lambda}\sqrt{\frac{Q\beta}{2R}}, \tag{50}$$

then $T_3 < T$. If the inequality (49) is realized and if $\chi(T) \to \infty$, then $T_3 \to 0$ for all fixed T.

Let T_2 be the time of transfer of the system, using $u=\nu(\eta,\chi)$, from the state on the line B at $t=T-T_3-T_2$ to the state on the line H at $t=T-T_3$. From the system (38) it is clear that T_2 is finite only for the initial values situated above the point A (see Fig.3.). Fixing $\chi(T)$ and integrating the system (34) in inverse time we can calculate values $\chi(0)$ and $\eta(0)$. In Fig. 6. the optimal trajectories for the initial values $\chi(0)=48.4$ are given.

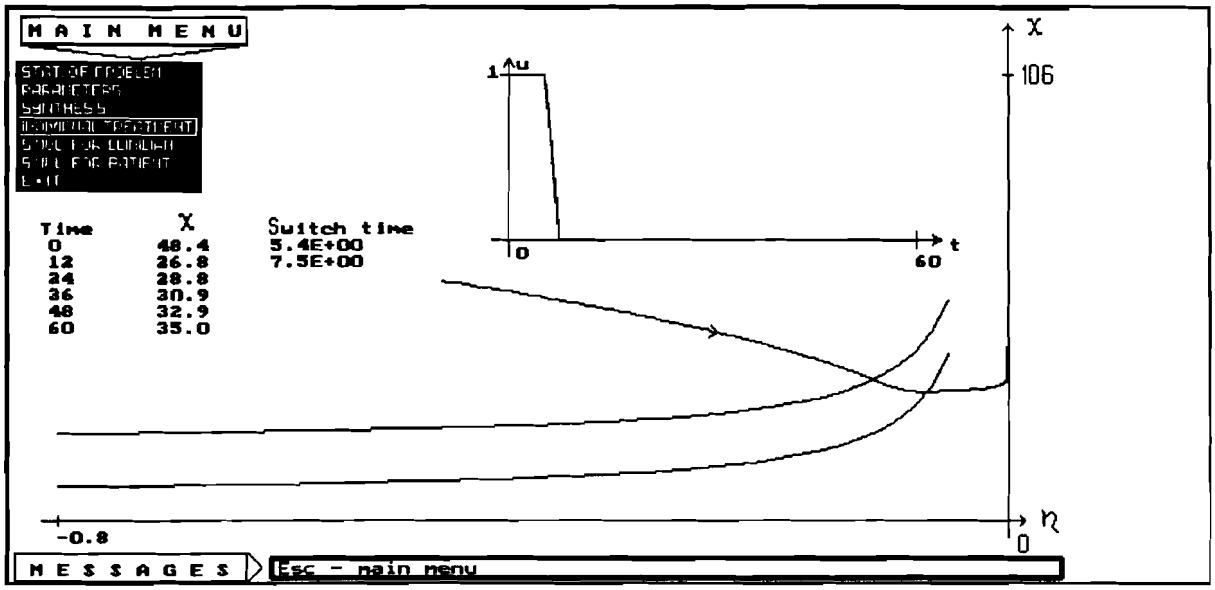

Figure 6 The result of the calculation by the option "Simulation for the clinician"

The solution of the synthesis problem is a basis for the development of the computer algorithms for the optimal drug administration problem. In Fig. 6 the menu of the program for the solution of the extremal problem (24),(25) and the example of optimal trajectory for the given initial value and corresponding control are given.

6. Discussion.

Here one special type of nonlinear control problem is discussed. The solution of this high dimensional problem may be transformed to the solution of the problem with smaller dimension. Similar problems with the additive control and the condition of invariant norm was studied by M. Athans and P.Falb.

Consider a problem

$$\frac{dx}{dt} = f(x,t,u), \qquad x(0) = x_0, \tag{51}$$

where $x \in R^n$, $u \in R^k$, $t \in [0,T]$, u(t) is measurable by Lebesgue function from the compact set $P \subset R^k$. Introduce absolute-continuous on [0,T] function z(t) from R^n. The problem is to calculate the appropriate control minimizing the functional

$$J_1(u) = \int_0^T (Q\| x(t) - z(t) \| + R\| u(t) \|) \, dt. \tag{52}$$

where $\| . \|$ is Euclidean norm.

Assumption 1. a) There exists the unique and positive continuating solution of (51); b) The solution of extremal problem (51),(52) exists; c) The function z(t) and a vector function f(x,t,u) satisfy the condition

$$(f(x(t),t,u(t)) - \dot{z}(t), x(t) - z(t)) = h(\| x(t) - z(t) \|, u(t),t) \tag{53}$$

for all t from [0,T] and all permissible control u(t) and corresponding x(t). Here $h(\| x(t) - z(t) \|,u,t)$ is a scalar continuous function.

Consider an extremum problem. We want to find measurable by Lebesque control

$u(t) \in P \subset R^k$ minimizing the functional

$$J_2(u) = \int_0^T (Qy(t) + R\| u \|) \, dt \tag{54}$$

under the condition

$$\begin{aligned} \dot{y} &= h_1(y,u,t), \qquad y(0) = y_0 = \| x_0 - z(0) \| \\ y &\in R^1,\ y>0,\ u \in P \subset R^k, \quad h_1(y,u,t) = \frac{h(y,u,t)}{y}. \end{aligned} \tag{55}$$

Assumption 2. a) There exist the unique and nonlokal continuating solution of (55); b) The solution of extremum problem (54),(55) exists.

Statement 4. Let $\bar{u}(t)$ be admissible control, $\bar{y}(t)$ and $\bar{x}(t)$ be corresponding trajectory of (55) and (51). Then under the Assumptions 1 and 2 $\bar{y}(t) = \| \bar{x}(t) - \bar{z}(t) \|$.

Proof. We have $\frac{d\bar{y}(t)}{dt} = h_1(\bar{y}(t),\bar{u}(t),t), \quad \bar{y}(0) = y_0 = \| x_0 - z_0 \|,$

$$\frac{d\bar{x}(t)}{dt} = f(\bar{x},\bar{u},t), \quad x(0) = x_0,$$

Introduce $\hat{y} = \| \bar{x}(t) - z(t) \|$. Then

$$\frac{d\hat{y}}{dt} = \frac{(\bar{x}(t) - z(t),\ f(\bar{x},\bar{u}(t),t) - \dot{z}(t))}{\| \bar{x}(t) - z(t) \|} = h_1(\| \bar{x}(t) - z(t) \|,\bar{u}(t),t) = \tag{56}$$

$$= h_1(\hat{y}(t),\bar{u}(t),t). \qquad \hat{y}(0) = \bar{y}(0) = \| x(0) - z(0) \|.$$

According to uniqness of the solution (55) $\bar{y}(t) = \hat{y}(t)$ almost everywhere.

Statement 5. If for the extremum problems (51),(52) and (54),(55) the assumptions 1 and 2 are satisfied and $\bar{u}(t)$ is a solution of (54),(55) then the minimum of the functional J_1 coincidence with minimum of functional J_2.

It means that the extremum control for the problem (51),(52) may be fined from the solution of (54),(55).

Remark. The nonlinear controlled system which satisfy the assumptions 1, 2 and z(t)=0 has the following structure $\frac{dx}{dt} = (\lambda(t,u,x)I + S(t,u,x))x + \Phi_1(t,u,x)$.

Here $x \in R^n$, I is a unit matrix, S(t,u,x) is n×n matrix such that $S(t,u,x) = -S^*(t,u,x)$ and the coefficients of this matrix continually depend on arguments. $\lambda(t,u,x)$ is a continuous function and $\Phi_1(t,u,x)$ is a function with components: $\frac{\varphi_i(t,u)}{x_i}$, $i = 1,...,n$,

where $\varphi_i(t,u)$ are continuous functions of arguments. The example of the dynamic

system which satisfy the assumptions 1,2 and can be transform to (55) is a model describing the competition two species for one resource

$$\begin{aligned} \frac{dx_1}{dt} &= -c(u)x_1 + f(x_1,x_2,u)x_2 + \frac{\varphi_1(t,u)}{x_1} \\ \frac{dx_2}{dt} &= -c(u)x_2 - f(x_1,x_2,u)x_1 - \frac{\varphi_2(t,u)}{x_2} \end{aligned} \tag{57}$$

where $\frac{\varphi_i(t,u)}{x_i} - c(u)x_i$ is a source rate; c(u) is a continuous function of argument;

$f(x_1,x_2,u)$ is a function describing the competition, for example $f(x_1,x_2,u) = (a - bx_1x_2)$; u(t) from [0,1] is a control variable.

Let $z(t) \in R^2$ be absolute continuous function on [0,T].The problem is to calculate the admissible control minimizing the functional

$$J(u(\cdot)) = \int_0^T (Q\| x(t) - z(t) \| + Ru(t))dt \tag{58}$$

where $x = (x_1,x_2) \in R^2$.

The problem (57),(58) satisfy the assumptions 1 and 2 and the solution of this problem can be calculated as a solution of bilinear control problem (24),(25) smaller dimension.

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