SECTION 2
PROBLEMS OF PARAMETER IDENTIFICATION IN MODELS OF PATHOLOGICAL PROCESSES

2.1. Problems of estimating parameters in Hilbert space for differential equations under uncertainty conditions

When modeling a number of processes of living nature [51,57,185], problems arise to find estimates of the parameters of systems that can be elements of some functional spaces. Such models include delayed differential equations, integro-differential equations, the theory of which is presented in papers [80,99]. The results on the identification of system parameters are presented in monographs [16, 56].

The purpose of this study is to establish the conditions for the existence of solutions to problems of identifying parameters given in abstract Hilbert spaces, as well as to build constructive algorithms for finding them.

The issue of the existence of optimal a posteriori estimates. Let be an observable vector-function $y(t) \in R^m$ of the form

$$y(t) = h(x(t,\alpha),t) + \eta(t),\ t_0 < t < T \tag{2.1.1}$$

with some previously unknown parameters α, and vector-functions $v(t)$. Suppose that a vector α belongs to some set G of Hilbert space H, and a vector function $\eta(t)$ belongs to a set G_η of Hilbert space $L_2(t_0,T)$, having the form

$$G_\eta = \left\{ v : \int_{t_0}^{T} \Phi(v,t)\,dt \le 1 \right\}, \tag{2.1.2}$$

where $\Phi(v,t)$ is a continuous, non-viable′function on $R^m \times [t_0,T]$, satisfying the condition

$$\Phi(v,t) \le C|v|^2, \tag{2.1.3}$$

where C is some constant.

If $h(x,t)$ is a continuous on a $R^n \times [t_0,T]$ function and such that there exists a constant C_1 such that

$$|h(x,t)| \le C_1|x|, \tag{2.1.4}$$

a $x(t,\alpha)$ belongs to the set $L_2(t_0,T)$ $\forall \alpha \in G$, then the posteriori set of possible values of the parameter α is defined as follows

$$G_y = G \bigcap G_1,$$

where

$$G_1 = \left\{ \alpha : \int_{t_0}^{T} \Phi\left(y(t) - h\left(x(t,\alpha),t\right),t\right)dt \le 1 \right\} \tag{2.1.5}$$

In the problems of a posteriori assessment, the following two problems are important.

1. Describe the set G_y.

2. Determine the "optimal" element from the set G_y.

The successful solution of′the second problem depends on the criterion according to which we will look for the "optimal" element. In this work, we will choose a criterion of the form

$$J(\alpha) = \int_{t_0}^{T} \Phi\left(y(t) - h\left(x(t,\alpha),t\right),t\right)dt, \tag{2.1.6}$$

and we will determine the optimal value from the condition

$$\inf_{\alpha \in G} J(\alpha) = J(\hat{\alpha}). \tag{2.1.7}$$

It is clear that if such elements $\hat{\alpha}$ exist, then they will fall into the set G_y.

Statement 2.1.1. Suppose that either the set G is a compact, a $x(t,\alpha)$ is a continuous function of its arguments, or G is a bounded weakly closed set, the functional $J_1(\alpha)=\int_{t_0}^{T}\Phi\left(y(t)-h\left(x(t),t\right),t\right)dt$ is weakly semi-continuous at the bottom, and $x(t,\alpha_n)$ weakly coincides in $L_2(t_0,T)$ to , $x(t,\alpha_0)$if α_n it weakly coincides to α_0 in . H

Then there is an optimal a posteriori assessment.

The proof is given in Appendix A.2**.**

Consequence. Let $h(x,t)=H(t)x$, $\Phi(x,t)=\left(Q(t)x,x\right)$, where $H(t)$ is a matrix with continuous elements, and is $Q(t)$ a positively defined matrix whose elements are continuous on $[t_0,T]$. Then there is an optimal a posteriori evaluation.

Note 2.1.1. The condition of the boundness of the set G can be replaced by the condition

$\lim_{\|\alpha\|\to\infty} J(\alpha)=\infty.$

Remark 2.1.2. If $J(\alpha)$ it is strongly convex by α, then the optimal posteriori assessment is the only one.

Let us consider further the case when $x(t,\alpha)$ is′the solution of the differential equation:

$$\frac{dx}{dt}=f(t,x,\alpha)+\int_{t_0}^{t}g\left(t,s,x(s),\beta\right)ds \tag{2.1.8}$$

$$x(t_0)=x_0 \tag{2.1.9}$$

where $x(t)\in R^n$, $\alpha\in H_1$, . $\beta\in H_2$Here H_1,H_2 are abstract Hilbert spaces.

Let's enter the notation

$$f_1(t,x,\theta) = f(t,x,\alpha) + \int_{t_0}^{t} g(t,s,x(s),\beta)ds, \quad \theta = \begin{pmatrix} \alpha \\ \beta \end{pmatrix}.$$

Suppose that the values of the parameters α and β - are unknown, and only their a priori sets -- G_α and G_β respectively are given.

To establish the conditions for the existence of a posteriori estimates in Hilbert space, let us consider several partial cases (2.1.8), (2.1.9).

The general case of a linear system. Consider the following system

$$\begin{cases} \dfrac{dx(t)}{dt} = A(t,\alpha)x(t) \\ x(t_0) = x_0 \end{cases} \tag{2.1.10}$$

where $x(t) \in C^1([0,T],R^n)$, $A(t,\alpha):[0,T]\times G \times C^1([0,T],R^n) \to C([0,T],R^n)$ is a linear operator with respect to $x(t)$.

Statement 2.1.2. Suppose that the conditions of Statement 2.1.1 are met with respect to the functional and a priori set and $x(t,\alpha)$ are the solution of the system (2.1.10), where the operator $A(\bullet,\bullet)$ is linear with respect to $x(t)$ and is such that

(i) $\|A(s,\alpha)\| \le k(s)$ at $\alpha \in G, \quad s \in [t_0,T]$;

(ii) for arbitrary $x(s) \in C^1([0,T],R^n)$, arbitrary $\alpha_0 \in G$ and $\alpha_n \xrightarrow[n\to\infty]{} \alpha_0$ takes place

$$\lim_{\alpha_n \to \alpha_0} \int_{t'}^{t''} \left[A(s,\alpha_n)x(s) - A(s,\alpha_0)x(s) \right] ds = 0 \tag{2.1.11}$$

Then on the set $\alpha \in G$ there is an optimal a posteriori estimate $\hat{\alpha}$.

The proof is given in Appendix A.2**.**

Consequence 1. If the operator $A(s,\alpha)$ is linear with respect to α then the condition (2.1.11) can be rewritten as

$$\lim_{\alpha_n \to \alpha_0} \int_{t'}^{t''} \left\| A(s,\alpha_n) - A(s,\alpha_0) \right\| ds = 0 \tag{2.1.12}$$

Consequence 2. If the operator $A(s,\alpha)$ is linear relative α to and independent of t, i.e. then $A(s,\alpha) = A(\alpha)$ the condition (2.1.11) can be rewritten as

$$\lim_{\alpha_n \to \alpha_0} \left\| A(\alpha_n) - A(\alpha_0) \right\| = 0 \tag{2.1.13}$$

Linear system with an integral nucleus. Consider the system

$$\begin{cases} \dfrac{dx(t)}{dt} = Ax(t) + \displaystyle\int_0^t K(t-s)x(s)ds \\ x(0) = x_0 \end{cases} \tag{2.1.14}$$

where the evaluated parameter α is an unknown integral nucleus $K(\bullet) \in G$.

Statement 2.1.3. Suppose that the conditions of Statement 2.1.1 regarding the functional and the a priori set are fulfilled and at the same time $x(t,K)$ is the solution of the system (2.1.14), where the matrix-valued function $K(s)$ belongs to the set G satisfying

(i) for arbitrary $K_0(s) \in G$ and $K_n \xrightarrow[n\to\infty]{} K_0$ takes place

$$\lim_{n\to\infty}\int_0^T \left\|K_n(\tau)-K_0(\tau)\right\|^2 d\tau = 0 \qquad (2.1.15)$$

Then there is an optimal a posteriori evaluation $\hat{K}$ on the set $K(\bullet)\in G$.

The proof is given in Appendix A.2**.**

Evaluation problems in Hilbert space. On the solutions of the system (2.1.8), (2.1.9), we will consider the following problems.

Problem 2.1.1. With known values of the function $x(s)$ and $\frac{dx(s)}{ds}$, $s\le T$ find the estimates of the parameters α and β.

Problem 2.1.2. With a given function $y(t)$ such that:

$$y(t)=h(t,x(t))+\eta(t),,\ t_0\le t\le T \text{ where } y\in R^m,$$

h - known vector function, $\eta(t)$ - some unknown function belonging to the set G_η from the space $L_2(t_0,T)$ find the estimates of the parameters α and β, and the evaluation of the function $x(s)$, $s\ge T$.

Let us first note that these problems fit into the problems of estimating solutions of differential equations in Hilbert spaces.

Indeed, if you introduce a function $\theta(t)$ with values in $H=H_1\times H_2$ as a solution to the equation

$$\frac{d\theta}{dt}=0,\theta(t_0)=\theta,$$

where the derivative is understood in a strong sense, then we get a system of equations

$$\begin{cases} \dfrac{dx(t)}{dt} = f_1\big(s, x(s), \theta(s)\big), \\ x(t_0) = x_0 \end{cases}$$

$$\frac{d\theta}{dt} = 0, \qquad \theta(t_0) = 0. \tag{2.1.16}$$

Thus, in the case of problem 1, we must find the estimate $\theta(t)$ as the solution of the differential equation by observing $x(t), t_0 < t < T$ what satisfies the equation (2.1.8).

In the case of the second problem, the problem of estimation θ is $x(s)$ reduced to estimating the solutions of the differential equation in the Hilbert space $R^n \times H$.

Therefore, it is advisable to first investigate the problems of estimating the parameters of the solution of the differential equation in Hilbert space.

Let us first consider the case of a linear differential equation in H:

$$\frac{dx}{dt} = A(t)x(t) + B(t)\, f_1(t) \tag{2.1.17}$$

$$x(t_0) = x_0,$$

where $A(t) \in \mathcal{L}(H, H)$, $f_1(t)$ is an unknown function with $L_2\big((t_0, T), F_1\big)$, where F_1 is some Hilbert space, $B(t) \in \mathcal{L}(F_1, H)$, norms $\|A(t)\|$ and $\|B(t)\|$ are - continuous functions, x_0 is an unknown vector with H.

Note that the generalized solution of equation (2.1.17) will be understood as the solution of the integral equation:

$$x(t)=\int_{t_0}^{t}A(s)x(s)ds+\int_{t_0}^{t}B(s)\,f_1(s)ds\,.$$

It is possible to show that such a solution exists and is a single one and is a continuous function.

Let the following observations be given:

$$y(t)=\mathcal{H}\left(t,y(\bullet),x(\bullet)\right)+\mathcal{D}(t)\,f_2(t),$$

where F_2, Y are some Hilbert spaces, $\left\|\mathcal{D}(t)\right\|$ -- continuous by t, f_2 -- unknown function from space F_2, $\mathcal{H}\left(t,y(\bullet),x(\bullet)\right)$ depends on observations $y(s), s<t$ and at fixed t and y is a reflection of space H in Y.

Let also the triple $\left(x_0, f_1(\bullet), f_2(\bullet)\right)$ belong to some set G of the Hilbert space $H\times L_2\left((t_0,T),F_1\right)\times L_2\left((t_0,T),F_2\right)$.

Definition. A posteriori estimation of the vector $Sx(T)$, where $S\in\mathcal{L}(H,F_3)$, F_3 is the Hilbert space, we call the vector $S\hat{x}(T)$, where $\hat{x}(T)$ is the solution of the equation

$$\frac{d\hat{x}}{dt}=A(t)\hat{x}(t)+B(t)\,\hat{f}_1(t),$$

$$\hat{x}(t_0)=\hat{x}_0,$$

and the pair $\left(\hat{x}_0,\hat{f}_1\right)$ belongs to a posteriori set G_y, defined as follows:

$$G_y=\left\{(x_0,f_1):(x_0,f_1,f_2)\in G_y^{(1)}\right\},$$

where

$$G_y^{(1)} = \left\{ (x_0, f_1, f_2) : (x_0, f_1, f_2) \in G, y(t) = \mathrm{H}\left(t, y(\bullet), x(\bullet)\right) + \mathrm{D}(t) f_2(t), t_0 \le t \le T \right\}$$

Obviously, if $\mathcal{H}\left(t, y(\bullet), x(\bullet)\right)$ is a continuous mapping and the set $\mu \in G_\mu$ is bounded, then the posteriori set is also bounded.

Note 2.1.1. If $\hat{x}_0$, $\hat{f}_1$ are a posteriori estimates of vectors x_0 and f_1, accordingly, then there is an inequality

$$\left\{ \left\| \hat{x}_0 - x_0 \right\|^2 + \left\| \hat{f}_1 - f_1 \right\|^2 \right\}^{1/2} \le \sup_{(x_0, f_1) \in G_y} \left[\left\| \hat{x}_0 - x_0 \right\|^2 + \left\| \hat{f}_1 - f_1 \right\|^2 \right]^{1/2} = \sigma_a^{(1)}$$

On the other hand, for minimax posteriori estimates $\hat{\hat{x}}_0$, $\hat{\hat{f}}_1$ defining from equality

$$\inf_{(\hat{x}_0, \hat{f}_1) \in G_y} \sup_{(x_0, f_1) \in G_y} \left\{ \left\| \hat{x}_0 - x_0 \right\|^2 + \left\| \hat{f}_1 - f_1 \right\|^2 \right\}^{1/2} = \sup_{(x_0, f_1) \in G_y} \left[\left\| \hat{\hat{x}}_0 - x_0 \right\|^2 + \left\| \hat{\hat{f}}_1 - f_1 \right\|^2 \right]^{1/2} = \sigma_a$$

The following inequality takes place

$$\sigma_a \le \sigma_a^{(1)}.$$

Remark 2.1.2. Let G be a bounded closed set. Then

$$\sup_{(x_0, f_1) \in G_y} \left[\left\| \hat{x}_0 - x_0 \right\|^2 + \left\| \hat{f}_1 - f_1 \right\|^2 \right]^{1/2} = \sup_{(l_1, l_1) + (l_2, l_2) \le 1} \left[\sigma_l + \left| L\left(\hat{f} \right) - \hat{L}\left(f \right) \right| \right]^{1/2}$$

where

$$\sigma_l = \frac{1}{2}\left[\sup_{G_y} L(f) - \inf_{G_y} L(f)\right] \qquad \hat{L}(f) = \frac{1}{2}\left[\sup_{G_y} L(f) + \inf_{G_y} L(f)\right]$$

$$L(f) = (l_1, x_0) + (l_2, f_1) \qquad L(\hat{f}) = (l_1, \hat{x}_0) + (l_2, \hat{f}_1)$$

The proof is given in Appendix A.2**.**

Note 2.1.3. Let the set G_y be bounded and closed, and centrally symmetric with respect to the vector $\overline{x}_0, \overline{f}_1$ (i.e., if $(x_0 - \overline{x}_0, f_1 - \overline{f}_1) \in G_y$ then and $-(x_0 - \overline{x}_0, f_1 - \overline{f}_1) \in G_y$). Then it is easy to see that

$$\sup_{G_y} L(f) = \sup_{\tilde{G}_y} L(f) + L(\overline{f})$$

$$\inf_{G_y} L(f) = -\sup_{\tilde{G}_y} L(f) + L(\overline{f})$$

where $\tilde{G}_y = G_y - (\overline{x}_0, \overline{f}_0)$ and is centrally symmetric with respect to zero and means

$$\sigma_a^{(1)} = \sup_{(l_1,l_1)+(l_2,l_2)\le 1}\left[\sup_{\tilde{G}_y} L(f) + \left|L(\hat{f}) - L(\overline{f})\right|\right] \ge \sup_{\tilde{G}_y}\left[(x_0, x_0) + (f_1, f_1)\right]^{1/2}$$

The equal sign is achieved at $\hat{f} = \overline{f}$. That is, $\overline{f}$ it is a minimax a posteriori estimate with an estimation error

$$\sigma_a = \sup_{\tilde{G}_y}\left[(x_0, x_0) + (f_1, f_1)\right]^{1/2}.$$

Next, consider the case when $\mathcal{H}(t, y(\bullet), x(\bullet))$ it depends on $x(\bullet)$ linearly, moreover

$$\mathcal{H}\left(t, y(\bullet), x(\bullet)\right) = \mathcal{H}\left(t, y(\bullet)\right) x(t) \tag{2.1.18}$$

where $\mathcal{H}\left(t, y(\bullet)\right) \in \mathcal{L}(H, Y)$.

Let's enter the functionality:

$$\mathcal{J}(x_0, f_1, f_2) = (Q_0 x_0, x_0) + \int_{t_0}^{T} (Q_1 f_1, f_1) dt + \int_{t_0}^{T} (Q_2 f_2, f_2) dt +$$
$$+ \int_{t_0}^{T} \left(\lambda(t), y(t) - \mathcal{H}\left(t, y(\bullet)\right) x(t) - \mathcal{D}(t) f_2(t) \right) dt$$

and consider the following a posteriori set:

$$G_y = \left\{ (x_0, f_1) : \mathcal{J}(x_0, f_1, f_2) \le 1 \right\} \tag{2.1.19}$$

Theorem 2.1.1. A posteriori estimates of the problem (2.1.17)-(2.1.19) can be found as a result of solving the following system of equations with respect to $p(t), \hat{x}(t), \hat{\lambda}(t)$

$$\begin{cases} -p'(t) - A^*(t) p(t) = \mathcal{H}^*\left(t, y(\bullet)\right) \hat{\lambda}(t), \\ p(T) = 0, \end{cases} \tag{2.1.20}$$

$$\begin{cases} \dfrac{d\hat{x}(t)}{dt} = A(t) \hat{x}(t) + B(t) Q_1^{-1} B^*(t) p(t), \\ \hat{x}(t_0) = Q_0^{-1} p(t_0), \end{cases} \tag{2.1.21}$$

$$y(t) = \mathcal{H}^*\left(t, y(\bullet)\right) \hat{x}(t) + \frac{1}{2} \mathcal{D}(t) Q_2^{-1} \mathcal{D}^*(t) \hat{\lambda}(t), \tag{2.1.22}$$

and have the following form

$$\hat{f}_1(t) = Q_1^{-1} B^*(t)\, p(t), \qquad \hat{f}_2(t) = \frac{1}{2} Q_2^{-1} \mathcal{D}^*(t) \hat{\lambda}(t). \tag{2.1.23}$$

The proof is given in Appendix A.2.

Theorem 2.1.2. Let there be $G = \left[\mathcal{D}(t) Q_2^{-1} \mathcal{D}^*(t) \right]^{-1}$. Then the solution of the system (2.1.20)-(2.1.22) can be found in the form

$$\hat{x}(t) = \mathcal{P}(t)\, p(t) + q(t) \tag{2.1.24}$$

where $q(t) \in R^n$ is the solution to the problem

$$\begin{cases} \dfrac{dq(t)}{dt} = A(t) q(t) + 2\mathcal{P}(t) \mathcal{H}^*\left(t, y(\bullet)\right) G\left[y(t) - \mathcal{H}\left(t, y(\bullet)\right) q(t) \right] \\ q(t_0) = 0, \end{cases} \tag{2.1.25}$$

operator $\mathcal{P}(t) \in \mathcal{L}\left(H, R^n\right)$ is the solution of the following Rikkati equation

$$\begin{cases} \dfrac{d\mathcal{P}(t)}{dt} = A(t)\mathcal{P}(t) + \mathcal{P}(t) A^*(t) - 2\mathcal{P}(t) \mathcal{H}^*\left(t, y(\bullet)\right) G \mathcal{H}\left(t, y(\bullet)\right) \mathcal{P}(t) + B(t) Q_1^{-1} B*(t) \\ \mathcal{P}(t_0) = Q_0^{-1}. \end{cases} \tag{2.1.26}$$

The proof is given in Appendix A.2**.**

Finally, consider the case of the differential equation (2.1.17) over the space $R^n \times H$, where is H the abstract Hilbert space, and the operator $\mathcal{H}\left(t, y(\bullet)\right)$ has the form $\mathcal{H}\left(t, y(\bullet)\right) = \left(H_1(t), \Theta\right)$, where $H_1(t) \in R^{m \times n}$, Θ is the null operator. Let

the vector $x(t) \in R^n \times H$ have a representation $x = \begin{pmatrix} x_1 \\ x_2 \end{pmatrix}$ of , where $x_1 \in R^n$, $x_2 \in H$.

Let us Y consider R^m and $Q_2 \in R^{m \times m}$. Then:

$$y(t) = H_1(t) x_1(t) + \mathcal{D}(t) f_2(t),$$

where $\mathcal{D}(t) f_2(t) \in R^m$.

Further, using the result [50] on the representation of the linear operator $A \in \mathcal{L}\left(R^n \times H, R^n \times H\right)$, where H is the abstract Hilbert space, in the form:

$A = \begin{pmatrix} A_{11} & A_{12} \\ A_{21} & A_{22} \end{pmatrix}$, where $A_{11} \in \mathcal{L}\left(R^n, R^n\right)$, $A_{12} \in \mathcal{L}\left(H, R^n\right)$ $\inf\limits_{G_\tau \times G_\mu} J(\tau, \mu) = J(\hat{\tau}, \hat{\mu}),,,$

$$, \; A_{22} \in \mathcal{L}(H, H)$$

Let's come to the following cleavages of operators:

$$A(t) = \begin{pmatrix} A_{11}(t) & A_{12}(t) \\ A_{21}(t) & A_{22}(t) \end{pmatrix}, \; \mathcal{P}(t) = \begin{pmatrix} P_{11}(t) & P_{21}(t) \\ P_{21}(t) & P_{22}(t) \end{pmatrix},$$

$$Q_1^{-1} = \begin{pmatrix} Q_1^{11} & Q_1^{12} \\ Q_1^{21} & Q_1^{22} \end{pmatrix}, \; B(t) = \begin{pmatrix} B_{11}(t) & B_{12}(t) \\ B_{21}(t) & B_{22}(t) \end{pmatrix},$$

where the elements of the operators belong to the corresponding spaces.

In this case, the problem (2.1.25) for $q(t) = \begin{pmatrix} q_1(t) \\ q_2(t) \end{pmatrix}$ is reduced to the following problems:

$$\begin{cases} \dfrac{dq_1(t)}{dt} = A_{11}(t) q_1(t) + A_{12}(t) q_2(t) + 2P_{11}(t) H_1^*(t) G\left[y(t) - H_1(t) q_1(t)\right] \\ q_1(t_0) = 0, \end{cases}$$

$$\begin{cases} \dfrac{dq_2(t)}{dt} = A_{21}(t)q_1(t) + A_{22}(t)q_2(t) + 2P_{21}(t)H_1^*(t)G\left[y(t) - H_1(t)q_1(t)\right] \\ q_2(t_0) = \Theta, \end{cases}$$

and four problems for the component of the operator $\mathcal{P}(t)$.

2.2. The problem of identifying the integral nucleus in observations at known states and derivatives of the system

Introduction and problem statement. When building models of a number of processes in biology and medicine [99,106,185] they encounter systems that include a continuously distributed delay in observations. General methods for identifying systems of this kind were developed in the works [16,56]. Thus, in [56] methods of estimation in Hilbert spaces were proposed. In the works [99,106] The type of integral nucleus can be chosen based on biological considerations and experimental data. Thus, there is a need for some universal methods for constructing estimates of the integral nucleus, guaranteeing their optimality in a certain sense. In this study, the approach of evaluating the integral nucleus as the Chebyshev center, i.e. the center of symmetry of a posteriori set, is implemented.

In this paper, we consider the case when we have some observations $y(t) \in R^m \;\; t \in [0,T]$ of the form:

$$y(t) = \int_0^t K(t-s)x(s)ds + f_2(t) \qquad (2.2.1)$$

where $f_2(t) \in C\left[[0,T], R^m\right]$ are unknown errors, $K(s) \in R^{m\times n}$, is $s \in [0,T]$ an unknown matrix function consisting of continuously differentiable elements. The following results will be based on the assumption that

$$\begin{cases} \dfrac{dK(s)}{ds} = F_1(s), \\ K(0) = K_0. \end{cases} \tag{2.2.2}$$

where $F_1(s) \in L_2\left[[0,T], R^{m\times n}\right]$ is the unknown matrix-valued function, $K_0 \in R^{m\times n}$ is the unknown constant matrix. Next, we will use the notation $K(F_1, K_0)(s)$ for the solution (2.2.2).

Values f_2, F_1, K_0 are limited by irregularities

$$\int_0^T (Q_2 f_2, f_2)dt + \gamma^2 sp\int_0^T F_1(t)F_1^{\mathrm{T}}(t)dt + \beta^2 sp K_0 K_0^{\mathrm{T}} \le 1 \tag{2.2.3}$$

that specify a priori set. Here $Q_2 \in R^{m\times m}, \gamma, \beta$ are the known positively defined matrix and positive constants, respectively.

The purpose of the work is to find a posteriori estimation of the integral nucleus $K(s)$, a posteriori set G_y and a posteriori error σ.

Let's first find a posteriori estimates K_0 and $F_1(s)$.

Statement 2.2.1. A posteriori estimates K_0 of observations ($F_1(s)$ 2.2.1) can be calculated as

$$\hat{K}_0 = \frac{1}{\beta^2}\psi^{\mathrm{T}}(0) \tag{2.2.4}$$

$$\hat{F}_1(s) = \frac{1}{\gamma^2}\psi^{\mathrm{T}}(s) \tag{2.2.5}$$

where $\psi \in C^1\left[[0,T], R^{m\times n}\right]$ is the matrix, which is the solution of the initial problem

$$\begin{cases} \dfrac{d\psi(s)}{ds} = \int_s^T Q_2\left[y(t) - \int_o^t \left[\hat{K}_0 + \int_0^{t-s_1} \hat{F}_1(s_3)ds_3 \right] x(s_1)ds_1 \right] x^{\mathrm{T}}(t-s)dt, \\ \psi(T) = \mathrm{O} \end{cases} \quad (2.2.6)$$

O - zero-matrix.

The proof is given in [194, p.4-5]**.**

Theorem 2.2.1. The posteriori set for the problem (2.2.1) -(2.2.3) can be described as

$$G_y = \left\{ (F_1, K_0) \in L_2\left([0,T], R^{m\times n}\right) \times R^{m\times n} : \left(\mathcal{P}\begin{pmatrix} F_1 - \hat{F}_1 \\ K_0 - \hat{K}_0 \end{pmatrix}, \begin{pmatrix} F_1 - \hat{F}_1 \\ K_0 - \hat{K}_0 \end{pmatrix} \right) \le 1-\alpha \right\}, \quad (2.2.7)$$

where $\mathcal{P} \in \mathcal{L}\left(L_2\left([0,T], R^{m\times n}\right) \times R^{m\times n}, L_2\left([0,T], R^{m\times n}\right) \times R^{m\times n} \right)$ is some positively defined operator, $\hat{F}_1, \hat{K}_0$ is given by (2.2.4), (2.2.5), $\alpha : 0 \le \alpha \le 1$ is a constant defined as

$$\alpha = J\left(\hat{F}_1, \hat{K}_0\right) = \int_0^T \left(Q_2\left(y(t) - \int_0^t K\left(\hat{F}_1\right)(t-s)x(s)ds \right), y(t) - \int_0^t K\left(\hat{F}_1\right)(t-s)x(s)ds \right) dt +$$
$$+\gamma^2 sp \int_0^T \hat{F}_1(t)\hat{F}_1^{\mathrm{T}}(t)dt + \beta^2 sp\hat{K}_0\hat{K}_0^{\mathrm{T}}$$

(2.2.8)

The proof is given in [194, p.6-7]**.**

Note 2.2.1. The posteriori set G_y (2.2.11) is symmetric with respect to $\left(\hat{F}_1, \hat{K}_0\right)$. Thus, together with , G_y we will use a set $\tilde{G}_y$ symmetric with respect to (O,O) where O is the zero-matrix, i.e.

$$\tilde{G}_y = \left\{ \left(\tilde{F}_1, \tilde{K}_0\right) \in L_2\left([0,T], R^{m\times n}\right) \times R^{m\times n} : \left(\mathrm{P}\begin{pmatrix} \tilde{F}_1 \\ \tilde{K}_0 \end{pmatrix}, \begin{pmatrix} \tilde{F}_1 \\ \tilde{K}_0 \end{pmatrix} \right) \le 1-\alpha \right\}. \tag{2.2.9}$$

Our next goal is to find the a posteriori set of the problem (2.2.1) -(2.2.3) for the integral nucleus $K(s)$.

Definition. The posteriori set of the problem (2.2.1) -(2.2.3) for the integral nucleus $K(s)$ is called

$$G_K = \left\{ K(\bullet) \in L_2\left([0,T], R^{m\times n}\right) : J\left(F_1, K_0\right) \le 1 \right\}$$

Theorem 2.2.2. The posteriori set of the problem (2.2.1) -(2.2.3) can be described as

$$G_K = \left\{ K(\bullet) \in L_2\left([0,T], R^{m\times n}\right) : \left(S^{-1}\left(K-\hat{K}\right), \left(K-\hat{K}\right)\right)^{1/2} \le (1-\alpha)^{1/2} \right\} \tag{2.2.10}$$

where $S \in \mathcal{L}\left(L_2\left([0,T], R^{m\times n}\right), L_2\left([0,T], R^{m\times n}\right)\right)$ is some positively defined linear operator, $\hat{K}(s)$- is given by (2.2.4), $\alpha : 0 \le \alpha \le 1$is the constant defined in (2.2.8).

The proof is given in [194, p.8-10]**.**

Theorem 2.2.3. The posteriori error $\sigma_a^{(1)}$ for the problem (2.2.1) -(2.2.3) based on the posteriori set G_y given by the expression (2.2.7) is

$$\sigma_a^{(1)} = \frac{1}{1-\alpha} \lambda_{max}(\mathcal{P}) \tag{2.2.11}$$

The proof is given in [194, pp. 10-11]**.**

A case of unknown constraints on the initial value of an integral nucleus. Next, consider the case of model (2.2.1), (2.2.2), where we do not have

any information about the unknown value K_0. That is, we consider the following constraints

$$J(F_1,K_0)=\int_0^T\left(Q_2\left(y(t)-\int_0^t K(t-s)x(s)ds\right),y(t)-\int_0^t K(t-s)x(s)ds\right)dt+$$
$$+\gamma^2 sp\int_0^T F_1(t)F_1^{\mathrm{T}}(t)dt\le 1 \qquad (2.2.12)$$

Statement 2.2.2. A posteriori estimates for K_0 and $F_1(s)$ from the problem (2.2.1), (2.2.2), (2.2.12) can be calculated as

$$\hat{K}_0=\int_0^T\int_s^T\left(y(t)-\int_0^t\int_0^{t-s_1}\hat{F}_1(s_2)ds_2x(s_1)ds_1\right)x^{\mathrm{T}}(t-s)dtds\left(\int_0^T\int_s^T\int_0^t x(s_1)ds_1x^{\mathrm{T}}(t-s)dtds\right)^{-1} \qquad (2.2.13)$$

$$\hat{F}_1(s)=-\frac{1}{\gamma^2}\psi(s) \qquad (2.2.14)$$

where $\psi\in C^1\left[[0,T],R^{m\times n}\right]$ is the matrix function, which is the solution to the initial problem

$$\begin{cases}-\dfrac{d\psi(s)}{ds}=\int_s^T Q_2\left(y(t)-\int_0^t\left(\hat{K}_0+\int_0^{t-s_1}\hat{F}_1(s_2)ds_2\right)x(s_1)ds_1\right)x^{\mathrm{T}}(t-s)dt,\\ \psi(T)=\mathrm{O}\end{cases} \qquad (2.2.15)$$

O - zero-matrix.

The proof is given in [194, pp. 12-13]**.**

A posteriori sets G_y, G_K and a posteriori error $\sigma_a^{(1)}$ for problems (2.2.1), (2.2.2), (2.2.12) has a form similar to that presented in theorems 2.2.1, 2.2.2, 2.2.3.

2.3. Approximate a posteriori estimates of the parameters of differential equations with Voltaire operators

In this subsection, algorithms for solving problem 2, posed in subsection 2.1 in the class of integro-differential equations, will be proposed.

Problem statement. Consider the case where we have some observations $y(t) \in R^m$, $t \in [0,T]$

$$y(t) = H(t)x(t) + f_2(t), \tag{2.3.1}$$

($x(t) \in R^n$, $H(t) \in R^{m \times n}$ is a known matrix, the elements of which are continuous on $[0,T]$ functions, $f_2(t) \in L_2\left[[0,T], R^m\right]$ - unknown functions) and $x(t)$ is the solution of the differential equation

$$\begin{cases} \dfrac{dx(t)}{dt} = Ax(t) + \int_0^t K(t-s)x(s)ds \\ x(0) = x_0 \end{cases}, \tag{2.3.2}$$

where $K(s) \in R^{n \times n}$, $s \in [0,T]$ is an unknown matrix function with continuous elements, $x_0 \in R^n$ is a known initial state, $A \in R^{n \times n}$ is a known matrix.

Suppose the values f_2, K are bounded by inequality

$$J(f_2, K) = \int_0^T (Q_2 f_2, f_2)dt + \gamma^2 sp \int_0^T \left(K(t) - \bar{K}(t)\right)\left(K(t) - \bar{\bar{K}}(t)\right)^T dt \le 1 \tag{2.3.3}$$

Here $Q_2 \in R^{m\times m}, \gamma$ - the positively defined matrix and the positive constant are known, respectively, $\bar{K}(s) \in R^{n\times n}$ - the matrix function with $C[0,T]$.

Further, without limiting generality, we will assume that $\bar{K} = \mathrm{O}$, i.e.:

$$J(f_2, K) = \int_0^T (Q_2 f_2, f_2)dt + \gamma^2 sp\int_0^T K(t)K^T(t)dt \le 1 \qquad (2.3.4)$$

Definition 2.3.1. A posteriori set for an integral nucleus K based on observations (2.3.1), system (2.3.2) and constraints (2.3.4) is called

$$G_K = \left\{K(\bullet) \in L_2([0,T], R^{n\times n}) : J^*(K) \le 1\right\}$$

Definition 2.3.2. For a posteriori estimate of the integral nucleus K based on observations (2.3.1), system (2.3.2) and constraints (2.3.4), we take the value

$$\hat{K}(s) = \arg\inf_K J^*(K),$$

where $J^*(K) = J(y - Hx, K)$.

Algorithm for finding the initial approximation of the kernel. Let's give some iterative algorithm to find kernel estimates. Suppose we have some estimate $K_n(s)$. Let $x_n(t)$ be the solution of the problem (2.3.2), corresponding $K_n(s)$ to , and $x_{n+1}(t) \in C^1([0,T], R^n)$ be the solution of the following equation

$$\begin{cases} \dfrac{dx_{n+1}(t)}{dt} = Ax_{n+1}(t) + \int_0^t K(t-s)x_n(s)ds, \quad n = 0,1,... \\ x_{n+1}(0) = x_0 \end{cases} \qquad (2.3.5)$$

with some $K(\bullet) \in L_2([0,T], R^{n\times n})$.

Let us denote the solution (2.3.5) corresponding to a specific kernel $K(\bullet)$ through $x_{n+1}(K)(t)$. Consider an approximate posteriori set:

$$G_K(n)=\left\{K: J_n(K)\le 1\right\} \tag{2.3.6}$$

where

$$\begin{aligned} J_n(K)=&\int_0^T\left(Q_2\left(y(t)-H(t)x_{n+1}(t)\right),y(t)-H(t)x_{n+1}(t)\right)dt+\\ &+\gamma^2 sp\int_0^T K(t)K^{\mathrm{T}}(t)dt \end{aligned} \tag{2.3.7}$$

We will find an approximate a posteriori assessment from the condition:

$$\hat{K}^{n+1}=\arg\inf_{K\in G_K(n)} J_n(K)$$

Lemma 2.3.1. The approximate a posteriori estimate of the integral nucleus $K(s),\quad s\in[0,T]$ for the problem (2.3.5)-(2.3.7) has the form

$$\hat{K}^{n+1}(s)=\frac{1}{\gamma^2}\int_s^T \psi_{n+1}(t)x_{n+1}^{\mathrm{T}}(t-s)dt,\ s\in(0,T] \tag{2.3.8}$$

where $\psi_{n+1}\in R^n$ is the solution of the boundary value problem

$$\begin{cases} \dfrac{dx_{n+1}(t)}{dt}=Ax_{n+1}(t)+\int_0^t \hat{K}^{n+1}(t-s)x_n(s)ds \\ x_{n+1}(0)=x_0 \end{cases} \tag{2.3.9}$$

$$\begin{cases} -\dfrac{d\psi_{n+1}(t)}{dt}-A^{\mathrm{T}}\psi_{n+1}(t)=H^{\mathrm{T}}(t)Q_2\left(y(t)-H(t)x_{n+1}(t)\right), \\ \psi_{n+1}(T)=\mathrm{O} \end{cases} \tag{2.3.10}$$

O - zero vector.

The proof is given in [213, p. 48]**.**

Search for an integral nucleus using a small parameter decomposition. Suppose further that the unknown nucleus $K(\bullet)$ can be given as

$$K(s) = K^0(s) + \varepsilon K^1(s) \tag{2.3.11}$$

where $K^0(s)$ is the known function and is $K^1(s) \in R^{n\times n}$ the unknown matrix function.

Let us denote the solution (2.3.2), which corresponds to (2.3.11) as $x(\varepsilon)$.

Let's put the following system of equations in accordance with the system (2.3.2) with the kernel $K(s)$ of the form (2.3.11)

$$\begin{cases} \dfrac{dx_1(t)}{dt} = Ax_1(t) + \int_0^t K_0(t-s)x_1(s)ds + \int_0^t K_1(t-s)\tilde{x}(s)ds \\ x_1(0) = 0 \end{cases} \tag{2.3.12}$$

where $\tilde{x}(\bullet) \in C^1([0,T], R^n)$ is the known solution of the main initial problem

$$\begin{cases} \dfrac{d\tilde{x}(t)}{dt} = A\tilde{x}(t) + \int_0^t K_0(t-s)\tilde{x}(s)ds \\ \tilde{x}(0) = x_0 \end{cases} \tag{2.3.13}$$

and

$$x_1(t) = \left.\frac{\partial x(\varepsilon)}{\partial \varepsilon}\right|_{\varepsilon=0}. \tag{2.3.14}$$

The approximate posteriori set is written in the form

$$G_{K^1}(\varepsilon)=\left\{K^1 : J_\varepsilon\left(K^1\right)\le 1\right\},$$

where

$$J_\varepsilon\left(K^1\right)=\int_0^T\left(Q\left[y(t)-H(t)\tilde{x}(t)-\varepsilon H(t)x_1(t)\right],\left[y(t)-H(t)\tilde{x}(t)-\varepsilon H(t)x_1(t)\right]\right)dt+$$
$$+\gamma^2 sp\int_0^T K^1(s)K^{1\mathrm{T}}(s)ds$$

where $\tilde{x}(t)$ is the solution of the problem (2.3.13), $x_1(t)$ is the solution of the problem (2.3.12). We will look for an approximate a posteriori estimate from the condition:

$$K^1=\arg\inf_{K^1\in G_{K^1}(\varepsilon)} J_\varepsilon\left(K^1\right) \tag{2.3.15}$$

Statement 2.3.1. An approximate posteriori estimate of the integral nucleus $K^1(s),\quad s\in[0,T]$ is

$$\hat{K}^1(s)=\frac{1}{\gamma^2}\int_s^T\psi(t)\tilde{x}^{\mathrm{T}}(t-s)dt,\ s\in[0,T] \tag{2.3.16}$$

where $\psi\in C^1\left[[0,T],R^n\right]$ is the solution of the main initial problem

$$\begin{cases}-\dfrac{d\psi(t)}{dt}-A^{\mathrm{T}}\psi(t)-\int_t^T K_0^{\mathrm{T}}(s-t)\psi(s)ds=\\ =-\varepsilon H^{\mathrm{T}}(t)Q_2\left[y(t)-H(t)x_0-\varepsilon H(t)x_1\left(\hat{K}^1\right)(t)\right]\\ \psi(T)=\mathrm{O}\end{cases} \tag{2.3.17}$$

O - zero vector.

The proof is given in [213, p. 50]**.**

Next, we consider the case when the nucleus $K^1(s)$ is differentiable, that is, there is a relationship

$$\begin{cases} \dfrac{dK^1(s)}{ds} = F_1(s), \\ K^1(0) = K_0^1. \end{cases} \tag{2.3.18}$$

where $F_1(s) \in L_2\left[[0,T], R^{n\times n}\right]$ is the unknown matrix value function, $K_0^1 \in R^{n\times n}$ is the unknown constant matrix. The approximate a posteriori set is given as:

$$G_{F_1(s),K_0^1} = \left\{\left(F_1(s), K_0^1\right) : J\left(F_1(s), K_0^1\right) \le 1\right\}$$

where

$$J\left(F_1(s), K_0^1\right) = \int_0^T \left(Q_2 f_2(t), f_2(t)\right)dt + \gamma^2 sp\int_0^T F_1(s)F_1^{\mathrm{T}}(s)ds + \beta^2 sp K_0^1 K_0^{1\mathrm{T}}$$

We will look for an approximate a posteriori estimate under the condition:

$$\left(\hat{F}_1(s), \hat{K}_0^1\right) = \arg \inf_{\left(F_1(s),K_0^1\right)\in G_{F_1(s),K_0^1}} J\left(F_1(s), K_0^1\right) \tag{2.3.19}$$

Statement 2.3.2. An approximate a posteriori estimation of the integral nucleus $K^1(s), \quad s \in [0,T]$ for the problem (2.3.18), (2.3.19) has the form

$$\hat{K}^1(s) = \hat{K}_0^1 + \int_0^s \hat{F}_1(s)ds \tag{2.3.20}$$

where $\hat{K}_0^1$ and $\hat{F}_1(s)$ are approximate a posteriori estimates for K_0^1 and $F_1(s)$ respectively. $\hat{K}_0^1$ and $\hat{F}_1(s)$ can be calculated as

$$\hat{K}_0^1 = \frac{1}{\beta^2}\psi(0), \quad \hat{F}_1(s) = \frac{1}{\gamma^2}\psi(s), \tag{2.3.21}$$

where $\psi \in C^1\left[[0,T], R^{n\times n}\right]$ is the matrix, which is the solution of the boundary value problem

$$\begin{cases} -\dfrac{d\psi(s)}{ds} = \int_s^T p(t)\tilde{x}^{\mathrm{T}}(t-s)dt, \\ \psi(T) = \mathrm{O} \end{cases} \tag{2.3.22}$$

O - zero-matrix, where $p(t) \in C^1\left([0,T], R^n\right)$ is the solution of the boundary value problem

$$\begin{cases} -\dfrac{dp(t)}{dt} - A^{\mathrm{T}}p(t) - \int_t^T K_0^{\mathrm{T}}(s-t)\,p(s)ds = \\ = -\varepsilon H^{\mathrm{T}}(t)Q_2\left[y(t) - H(t)x_0 - \varepsilon H(t)x_1\left(\hat{F}_1\right)(t)\right], \\ p(T) = 0 \end{cases} \tag{2.3.23}$$

The proof is given in [213, p. 51-52]**.**

Combining statements 2.3.1 and 2.3.2, we get the following result.

Comments. An approximate a posteriori estimate of the integral nucleus $K(s), \quad s \in [0,T]$ for the problem (2.3.1), (2.3.2) with a small parameter ε can be found as

$$\hat{K}(s) = \hat{K}_0(s) + \varepsilon \hat{K}_1(s) \tag{2.3.24}$$

where $\hat{K}_0(s)$ is some initial approximation. $\hat{K}_1(s)$ is calculated according to (2.3.16) in the case of constraints (2.3.15). If the integral kernel is differentiable and we have constraints (2.3.18), (2.3.1923), then $\hat{K}_1(s)$ we use (2.3.20), (2.3.21) for the calculation.

2.4. Identification of parameters of systems with a delay

A system of nonlinear differential equations with a delay in the argument is considered:

$$\begin{cases} \dfrac{dx(t)}{dt} = f(t, x(t), x(t-\tau), \mu), t > t_{0,} \\ x(t) = \varphi(t),\ t \in (t_0 - \tau, t_0). \end{cases} \tag{2.4.1}$$

At $x(t) \in R^m$, $\tau > 0$ is a constant delay, $\mu \in R^m$ are the parameters of the system. We assume that there is a single solution (2.4.1) in the class of continuously-differentiable functions on the interval $t \in [t_0, T], T > t_0$.

The identification task for the system (2.4.1) is to find the parameters $\mu \in G_\mu$ and the magnitude of the delay $\tau \in G_\tau$ if the function of the form is observed $t \in [t_0, T]$ on the interval:

$$y(t) = H(t)x(t) + v(t),$$

where $H(t)$ is the matrix function, $v(t)$ is an unknown vector function, such that the condition is met:

$$\int_{t_0}^{T} \Phi\left(t, v(t)\right) dt \le 1,$$

where $\Phi(t,v) \ge 0$ is a continuous function by variables.

The posteriori set to which the parameters τ and μ, belong, will be of the form

$$G_y = \left\{ (\tau, \mu) : \int_{t_0}^{T} \Phi\left(t, y(t) - H(t,\tau,\mu) x(t)\right) dt \le 1 \right\}.$$

For a posteriori assessment of parameters, we take the values $\hat{\tau}$ and $\hat{\mu}$ such that:

$$\inf_{G_\tau \times G_\mu} J(\tau, \mu) = J(\hat{\tau}, \hat{\mu})$$

where

$$J(\tau, \mu) = \int_{t_0}^{T} \Phi\left(t, y(t) - H(t) x(t, \tau, \mu)\right) dt . \qquad (2.4.2)$$

Here $x(t, \mu, \tau)$ is the solution of the system (2.4.1) at the given values and μ τ. Note that such $\hat{\tau}$ and $\hat{\mu}$ exist when G_τ and G_μ are compact sets, and the solution of the system (2.4.1) $x(t, \tau, \mu)$ continuously depends on the parameters τ and μ.

Next, we assume that for the system (2.4.1) the conditions of differentiation by parameters μ and τ [50] are met.

Definition 2.4.1. The system sensitivity function (2.4.1) with respect to parameters $\mu \in R^m$ is called the matrix function

$$U_{\mu}(t,\mu,\tau)=\left\{\frac{\partial x_i(t,\mu,\tau)}{\partial \mu^j}\right\},i=\overline{1,n},\ j=\overline{1,m}$$

Definition 2.4.2. The sensitivity function of the system (2.4.1) relative to the value of the delay τ is called the vector function

$$U_{\tau}(t,\mu,\tau)=\left(\frac{\partial x_i(t,\mu,\tau)}{\partial \tau}\right)_{i=\overline{1,n}}$$

Lemma 2.4.1. Sensitivity functions $U_{\mu}(t,\mu,\tau)$ and $U_{\tau}(t,\mu,\tau)$ can be found from the following initial problems:

$$\begin{cases}\dfrac{dU_{\mu}(t,\mu,\tau)}{dt}=\left.\dfrac{\partial f(t,x,x(t-\tau),\mu)}{\partial x}\right|_{x=x(t)}U_{\mu}(t,\mu,\tau)+\left.\dfrac{\partial f(t,x(t),y,\mu)}{\partial y}\right|_{y=x(t-\tau)}U_{\mu}(t-\tau,\mu,\tau)+\\ +\dfrac{\partial f(t,x(t),x(t-\tau),\mu)}{\partial \mu},t>t_0\\ U_{\mu}(t)\equiv 0,\quad t\in[t_0-\tau,t_0]\end{cases}$$

(2.4.3)

$$\begin{cases}\dfrac{dU_{\tau}(t,\mu,\tau)}{dt}=\left.\dfrac{\partial f(t,x,x(t-\tau),\mu)}{\partial x}\right|_{x=x(t)}U_{\tau}(t,\mu,\tau)+\\ +\left.\dfrac{\partial f(t,x(t),y,\mu)}{\partial y}\right|_{y=x(t-\tau)}U_{\tau}(t-\tau,\mu,\tau),t>t_0\\ U_{\tau}(t)\equiv 0,t\in[t_0-\tau,t_0]\end{cases}$$

(2.4.4)

The proof follows by differentiating the system (2.4.1) for μ and τ respectively and using the definitions 2.4.1 and 2.4.2.

When solving the problem of identifying system parameters (μ,τ) (2.4.1), we assume that some initial approximations are given (μ_0,τ_0).

We will use the following iterative procedure:

$$\begin{aligned}&\hat{\mu}_{i+1}=\hat{\mu}_i+\Delta\mu_i;\\&\hat{\tau}_{i+1}=\hat{\tau}_i+\Delta\tau_i, i=0,1,2\ \ ...\end{aligned} \tag{2.4.5}$$

Here $(\hat{\mu}_i,\hat{\tau}_i), i=1,2,...$ are the estimates of the parameters and the magnitude of the delay, $(\Delta\mu_i,\Delta\tau_i), i=1,2,...$ the increments that will be determined at each step. In this case, it is necessary to check the fulfillment $\hat{\tau}_i>0$ of the condition or use the method of conditional optimization (for example, penalty functions).

To determine the magnitude of the increases $(\Delta\mu_i,\Delta\tau_i)$, we will use the first approximation:

$$\begin{aligned}&x(t,\hat{\mu}_i+\Delta\mu_i,\hat{\tau}_i)\approx x(t,\hat{\mu}_i,\hat{\tau}_i)+U_\mu(t,\hat{\mu}_i,\hat{\tau}_i)\Delta\mu_i;\\&x(t,\hat{\mu}_i,\hat{\tau}_i+\Delta\tau_i)\approx x(t,\hat{\mu}_i,\hat{\tau}_i)+U_\tau(t,\hat{\mu}_i,\hat{\tau}_i)\Delta\tau_i;\end{aligned} \tag{2.4.6}$$

Theorem 2.4.1. Suppose that the function $\Phi(t,v)$ is differentiable by the second variable

Then the magnitudes of the increments $(\Delta\mu_i,\Delta\tau_i)$ can be found from the equations

$$\begin{aligned}
&\int_{t_0}^{T} \left.\frac{\partial \Phi(t,v)}{\partial v}\right|_{v=y(t)-H(t)\left(x(t,\hat{\mu}_i,\hat{\tau}_i)+U_\mu(t,\hat{\mu}_i,\hat{\tau}_i)\Delta\mu_i\right)} H(t)U_\mu(t,\hat{\mu}_i,\hat{\tau}_i)dt = 0 \\
&\int_{t_0}^{T} \left.\frac{\partial \Phi(t,v)}{\partial v}\right|_{v=y(t)-H(t)\left(x(t,\hat{\mu}_i,\hat{\tau}_i)+U_\tau(t,\hat{\mu}_i,\hat{\tau}_i)\Delta\tau_i\right)} H(t)U_\tau(t,\hat{\mu}_i,\hat{\tau}_i)dt = 0
\end{aligned} \tag{2.4.7}$$

relative to $\Delta\mu_i$ and $\Delta\tau_i$, provided that such solutions exist.

The proof is given in Appendix A.2**.**

Consequence 2.4.1. Let the function $\Phi(t,v) = v^T v$ and at the same time be given observations $\|H(t)\| \le H$. Suppose that with given parameter estimates, the $(\hat{\mu}_i, \hat{\tau}_i)$ system (2.4.1) is such that :

$$\begin{aligned}
&1) \det \int_{t_0}^{T} U_\mu^T(t,\hat{\mu}_i,\hat{\tau}_i)U_\mu(t,\hat{\mu}_i,\hat{\tau}_i)dt \neq 0, \\
&2) \det \int_{t_0}^{T} U_\tau^T(t,\hat{\mu}_i,\hat{\tau}_i)U_\tau(t,\hat{\mu}_i,\hat{\tau}_i)dt \neq 0
\end{aligned} \tag{2.4.8}$$

Then the magnitudes of the gains $(\Delta\mu_i, \Delta\tau_i)$ can be found from the formulas:

$$\begin{aligned}
\Delta\mu_i &= \left(\int_{t_0}^{T} U_\mu^T(t,\hat{\mu}_i,\hat{\tau}_i)U_\mu(t,\hat{\mu}_i,\hat{\tau}_i)dt\right)^{-1} \cdot \int_{t_0}^{T} U_\mu^T(t,\hat{\mu}_i,\hat{\tau}_i)(x_э(t) - x(t,\hat{\mu}_i,\hat{\tau}_i))dt \\
\Delta\tau_i &= \left(\int_{t_0}^{T} U_\mu^T(t,\hat{\mu}_i,\hat{\tau}_i)U_\tau(t,\hat{\mu}_i,\hat{\tau}_i)dt\right)^{-1} \cdot \int_{t_0}^{T} U_\tau^T(t,\hat{\mu}_i,\hat{\tau}_i)(x_э(t) - x(t,\hat{\mu}_i,\hat{\tau}_i))dt
\end{aligned} \tag{2.4.9}$$

The proof follows directly from theorem 2.4.1. We only note that the conditions (2.4.8) are the conditions for the existence of solutions to equations (2.4.7).

Lemma 2.4.2. Suppose that the system (2.4.1) satisfies the following inequalities at $t \in [t_0, T]$:

$$\left\| \left. \frac{\partial f\left(t, x, x(t-\tau), \mu\right)}{\partial x} \right|_{x=x(t)} \right\| \le a, \quad \left\| \left. \frac{\partial f\left(t, x(t), y, \mu\right)}{\partial y} \right|_{y=x(t-\tau)} \right\| \le b$$

$$\left\| \frac{\partial f}{\partial \mu} \right\| \le c, \left\| \frac{\partial f}{\partial \tau} \right\| \le d, \quad \left\| R_\mu \right\| \le h_\mu, \quad \left\| R_\tau \right\| \le h_\tau$$

where $a, b, c, d, h_\mu, h_\tau$ are some steels.

Here R_μ and R_τ are --nonlinear expressions with respect to second-order sensitivity functions that arise in computation $U_\mu^{(2)}(t)$ and $U_\tau^{(2)}(t)$:

$$\begin{cases} \dfrac{dU_\mu^{(2)}(t)}{dt} = \dfrac{\partial f}{\partial x(t)} U_\mu^{(2)}(t) + \\ + \dfrac{\partial f}{\partial x(t-\tau)} U_\mu^{(2)}(t-\tau) + R_\mu(t, x(t), x(t-\tau), U_\mu(t), U_\mu(t-\tau), \mu, \tau), t > t_0 \\ U_\mu^{(2)}(t) = 0, t \le t_0 \end{cases} \tag{2.4.10}$$

$$\begin{cases} \dfrac{dU_\tau^{(2)}(t)}{dt} = \dfrac{\partial f}{\partial x(t)} U_\tau^{(2)}(t) + \dfrac{\partial f}{\partial x(t-\tau)} U_\tau^{(2)}(t-\tau) + \\ + R_\tau(t, x(t), x(t-\tau), U_\tau(t), U_\tau(t-\tau), \mu, \tau), t > t_0 \\ U_\tau^{(2)}(t) = 0, t \le t_0 \end{cases} \tag{2.4.11}$$

Then the following assessments take place

$$\left\| x(t, \hat{\mu}_{i+1}, \hat{\tau}_i) - x(t, \hat{\mu}_i, \hat{\tau}_i) - U_\mu(t, \hat{\mu}_i, \hat{\tau}_i) \Delta\mu_i \right\| \le \frac{\Delta\mu_i^T \Delta\mu_i}{2} \cdot \left[\frac{h_\mu}{a+b} e^{(a+b)(t-t_0)} - \frac{h_\mu}{a+b} \right]$$

(2.4.12)

$$\left\| x(t,\hat{\mu}_i,\hat{\tau}_{i+1}) - x(t,\hat{\mu}_i,\hat{\tau}_i) - U_\tau(t,\hat{\mu}_i,\hat{\tau}_i)\Delta\tau_i \right\| \le \frac{\Delta\tau_i^2}{2}\cdot\left[\frac{h_\tau}{a+b}e^{(a+b)(t-t_0)} - \frac{h_\tau}{a+b}\right]$$

(2.4.13)

The proof is given in [176, pp. 259-260]**.**

Theorem 2.4.2. Let the conditions of the lemma 2.4.2 be fulfilled for the system (2.4.1). In addition, let there be a positive constant H, such that $\left\|H(t)\right\|_M \le H$, $t\in[t_0,T]$, is $\left\|\bullet\right\|_M$ any matrix norm, and the function $\Phi\left(t,v(t)\right)$ satisfies the $t\in[t_0,T]$ Lipschitz condition for the second variable in between, i.e. there is a constant $L>0$ such that $\left|\Phi\left(t,v_1(t)\right)-\Phi\left(t,v_2(t)\right)\right| \le L\left\|v_1(t)-v_2(t)\right\|$, $t\in[t_0,T]$. Then the following estimates take place:

$$\left|J\left(\tau_{i+1},\mu_i\right)-J\left(\tau_i,\mu_i\right)\right| \le \frac{LHh_\tau}{2(a+b)}\left\{\frac{e^{(a+b)(T-t_0)}-1}{a+b}-T+t_0\right\}\Delta\tau_i^2$$

(2.4.15)

$$\left|J\left(\tau_i,\mu_{i+1}\right)-J\left(\tau_i,\mu_i\right)\right| \le \frac{LHh_\mu}{2(a+b)}\left\{\frac{e^{(a+b)(T-t_0)}-1}{a+b}-T+t_0\right\}\Delta\mu_i^T\Delta\mu_i$$

The proof follows using inequality for the functionality $J\left(\tau,\mu\right)$ (2.4.12).

2.5. Overview of algorithms used to model changes in bone tissue

Cells of biological tissues have the unique property of changing the tissue matrix in response to environmental influences. This ability to adapt is not only impressive from a scientific point of view, but also has important clinical implications. If the adaptive capacity becomes unbalanced, for example, in the case of osteoporosis, this leads to the formation of tissues that are not able to withstand

functional loads and fractures. Interest in both identifying mechanisms and predicting tissue adaptation in clinical applications has led to the development of numerical models to predict bone adaptation.

Bone morphology. Bone tissue consists of cellular elements interconnected by a special substance called matrix [65]. Bone cells include:

- Osteoclasts are primary cells that resorb (destroy) bone. They can be in active and inactive states.
- osteoblasts are cells responsible for the production of bone matrix and its mineralization, as well as for structural ordering. In addition, they can act as intermediaries in the transmission of signals to osteoclasts.
- monocytes and macrophages - can be considered as non-bone cells, but they play a role in bone resorption, in particular, they destroy tissue residues that have not destroyed osteoclasts.

The matrix is an extracellular tissue, which is a biphasic material that consists of about 35% organic matrix and about 65% inorganic mineral.

General adaptation mechanisms. It has been experimentally established that bone tissue responds to external influences either by growing in length and width (osteogenesis), or by shaping (modelling), or by internal restructuring (reconstruction, remodelling) [65].

Osteogenesis occurs during embryonic development, in the early stages of growth, as well as during recovery during treatment. Bone is formed on soft tissue. In this case, osteoblasts originating from mesenchymal cells act independently of osteoclasts. There is the potential to create large areas of bone.

Formation occurs during growth and during recovery. Bone is formed on existing bone tissue. Osteoclasts and osteoclasts act independently in different places. There is the potential to create or destroy large areas of bone.

Internal restructuring occurs from bone growth throughout life. Bone is both formed and destroyed in the same place. This is the only normal physiological

mechanism for bone changes in adults. Under favorable circumstances, it leads to bone preservation. However, with aging, bone is somewhat lost.

Factors affecting the adaptation of bone tissue. Increased resorption is caused by the presence of parathyroid hormone, prostaglandins, glucocorticoids, thyroid hormones, etc.

Activation of bone tissue formation can be caused by calcitonin, vitamin D3, sex hormones (estrogens, androgens, progestins), bisphosphonates, sodium fluoride.

The effect of exposure to cytokines and growth factors depends on the cell-cell, cell-matrix interaction, the degree of differentiation of target cells, and can be both resorbing and forming.

The main hormones traditionally considered regulators of calcium metabolism and bone condition are calcitonin and parathyroid hormone.

Calcitonin is secreted by thyroid C-cells in response to an increase in Ca in the blood. It is a powerful direct inhibitor of osteoclastic activity and the formation of osteoclasts.

Parathyroid hormone is a potential bone resorption hormone that increases the number and activity of osteoclasts, which leads to the release of Ca and P from the mineral matrix, enhances the reabsorption of Ca in the kidneys, enhances the absorption of Ca in the small intestine (in the presence of vitamin D3), and regulates the excretion of P through the kidneys. The amount of parathyroid hormone in the blood is regulated directly by the level of Ca in the blood.

Mathematical theories of adaptation mechanisms. The first successful mathematical theories regarding the relationship between bone adaptation and mechanical stimuli appeared in the 1970s. The basic concepts of all mathematical and numerical theories of adaptation are based on an equation describing the evolution of bone structure, using the current bone structure and the existing mechanical state [93,94]:

$$\rho(t+\Delta t) = f(\rho(t), \sigma(t), \varepsilon(t)).$$

Here $\rho(t+\Delta t)$ are the parameters of the bone structure (most often bone density is taken) at the current moment of time $t+\Delta t$, $\rho(t)$ - the previous bone density at the time t, $\sigma(t)$ - the amount of bone compression at the time t, $\varepsilon(t)$ - the amount of bone stretch at the time t. When the bone structure changes, the mechanical properties of the bone also change, characterized by the following structural and functional dependence:

$$c^{eff} = c^{eff}(c^{micro}, M(\rho(t+\Delta t))).$$

Here c^{eff} is the effective strength, which depends on the microstructural strength and on the degree of orderliness of materials of different strengths, which is given by the matrix M, which is a function of the structure at the moment $t+\Delta t$. Since the properties of the material change, the compressive and tensile fields of the bone will change even when the load is constant. In this case, the compression and tensile fields are built in the form of

$$\sigma(t), \varepsilon(t) = f(c^{eff}, t, b). \qquad (2.5.1)$$

They can be found from equations

$$\frac{\partial}{\partial x_i}(c_{ijkl}^{eff}\varepsilon_{kl}(t+\Delta t))+b=0. \qquad (2.5.2)$$

Equations (2.5.1) and (2.5.2) simulate the physiological process of bone adaptation. Here b are mechanical signals filtered through tissues up to the level of bone cells. Bone cells sense mechanical signals and determine through special mechanisms whether these signals belong to the range of homeostatic perception.

For numerical simulation of bone adaptation, most of the numerical methods for calculating the compression-tensile medium are based on the finite element method. The most important thing that differs in numerical modeling of bone adaptation is the assumption of how the structure of the bone changes in the current mechanical environment.

Next, various theories about the mechanical environment of bone structure that have been proposed to model bone adaptation will be presented.

Algorithm of S. Kovin. The first prominent theory was developed by S. Kovin in 1976. The result of this theory was the following relationship between changes in the structure of bone tissue and mechanical stress [94]:

$$\dot{e}=\frac{de}{dt}=a(e)+A_{ij}(e)\varepsilon_{ij}+\frac{1}{2}B_{ijkl}(e)\varepsilon_{ij}\varepsilon_{kl}.$$

Here e is a measure of bone structure (mainly bone density), a, A_{ij}, B_{ijkl} - reconstruction tensors, which should be determined experimentally, ε_{ij} - tension. Note that reconstruction tensors depend on the current bone structure. It is also theoretically possible that reconstruction tensors take into account the state of the skeleton, i.e. whether modeling or reconstruction is possible.combine the equations

already discussed, namely structural-functional relationships, with the equations of elasticity. Next, it is necessary to iterate between:

1) reconstruction equations to obtain structures based on compression-tensile fields;
2) structural and functional relationships to obtain strength based on structure;
3) elasticity equations to obtain compression-tensile fields using strength.

Using a program based on the finite element method and previous equations, it is found that it is very difficult to determine the reconstruction constants, although the qualitative results are good.

So, finally, Covin's algorithm for modeling bone adaptation looks like this:

1. Change the structure of the bone

$$e(t+\Delta t) = e(t) + \Delta t\left[a(e(t)) + A_{ij}\varepsilon_{ij}(t) + \frac{1}{2}B_{ijkl}\varepsilon_{ij}(t)\varepsilon_{kl}(t) \right]$$

2. Change the effective strength of the bone based on the altered bone structure:

$$c^{eff} = f(e(t+\Delta t), c) \Rightarrow E = a\rho^{b}$$

3. Solve the equation of equilibrium with new strength to determine the new compressive-tensile fields:

$$\frac{\partial}{\partial x}\left(c^{eff}(t+\Delta t)\varepsilon(t+\Delta t) \right) = 0$$

4. Go back to step 1 and change the bone structure. Repeat until convergence is achieved.

Figri's algorithm. The next approach to bone adaptation was proposed by Figree and Carter in 1984. According to this approach, the goal of bone adaptation is to optimize the bone structure so that the compression measure is limited at the top to some fixed number.

$$\rho \to \min$$
$$Q(\rho, \sigma, \theta) \le Q_{\max}$$

Here ρ is bone density, Q is a measure of bone compression, such as Mises compression, $Q_{\max}$ is the limit of acceptable compression in bone tissue. In Figri's approach to modeling bone adaptation, the numerical algorithm would look like this:

1. Change the structure of the bone

$$\rho_{n+1} = \left(\frac{\sigma_p^T F_n \sigma_p}{Q_{\max}} \right)^{\frac{1}{B}}$$

Here

$$F_n = \begin{bmatrix} 1 & -\frac{1}{2} & -\frac{1}{2} \\ -\frac{1}{2} & 1 & -\frac{1}{2} \\ -\frac{1}{2} & -\frac{1}{2} & 1 \end{bmatrix},$$

σ_p - fundamental compression, B - a coefficient of structural-functional relationship.

2. Change the effective strength of the bone based on the altered bone structure:

$$c^{eff} = f(\rho(t+\Delta t), c) \Rightarrow E = a\rho^b$$

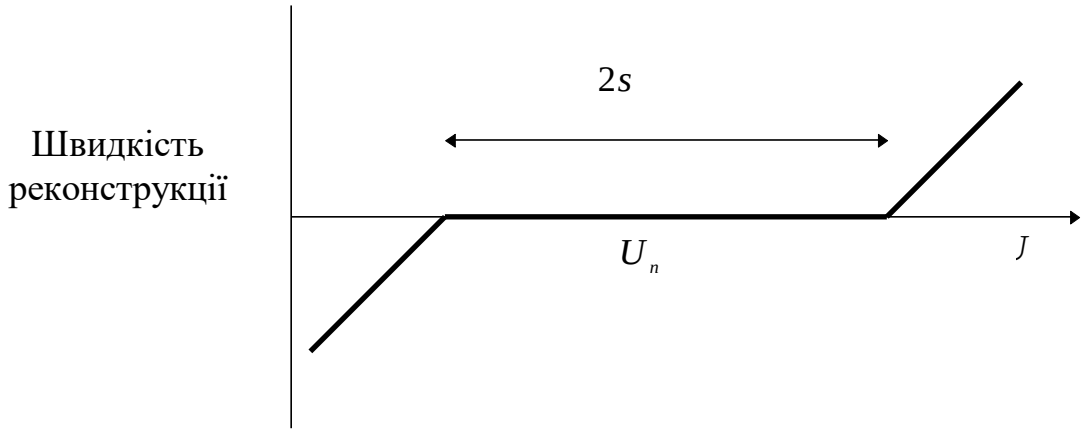
3. Solve the equation of equilibrium with new strength to determine the new compressive-tensile fields:

$$\frac{\partial}{\partial x}\left(c^{eff}(t+\Delta t)\varepsilon(t+\Delta t)\right) = 0$$

4. Go back to step 1 and change the bone structure. Repeat until convergence is achieved.

Using the algorithm proposed above for different matrices F, Figri was able to predict the distribution of bone density in the femoral head.

A third approach to modeling bone adaptation was proposed by Huyskes in 1987 [105]. This approach is again a continuation of Covin's approach, but it includes tensile energy density as a mechanical stimulus and a "zone of inactivity". The zone of inactivity is the interval of tensile energy densities for which no adaptation of the bone occurs. The concept of an inactivity zone can be graphically illustrated as follows:



Rice. 2.5.1. Zone of inactivity

Using the concept of the zone of inactivity, the equation of evolution of the structure of the tissue will take the form:

$$\frac{d\rho}{dt} = K(U - (1+s)U_n) \text{ if } U \geq (1+s)U_n$$
$$\frac{d\rho}{dt} = 0 \quad \text{if } (1-s)U_n \leq U \leq (1+s)U_n$$
$$\frac{d\rho}{dt} = K(U - (1-s)U_n) \quad \text{if } U \leq (1-s)U$$

Here ρ is the density of the bone, U is the current tensile energy density, U_n is the target tensile energy density, s is the width of the inactivity zone, K is the constant of the reconstruction. So, Huyskes proposed the following algorithm for modeling bone adaptation:

1. Change the structure of the bone, taking into account the ingress of tensile energy density into the zone of inactivity:

$$\rho(t+\Delta t) = \rho(t) + \Delta t K(U - (1+s)U_n) \text{ if } U \geq (1+s)U_n$$
$$\rho(t+\Delta t) = \rho(t) \quad \text{if } (1-s)U_n \leq U \leq (1+s)U_n$$
$$\rho(t+\Delta t) = \rho(t) + \Delta t K(U - (1-s)U_n) \quad \text{if } U \leq (1-s)U_n$$

2. Change the effective strength of the bone based on the altered bone structure:

$$c^{eff} = f(\rho(t+\Delta t), c) \Rightarrow E = a\rho^b$$

3. Solve the equation of equilibrium with new strength to determine the new compressive-tensile fields:

$$\frac{\partial}{\partial x}\left(c^{eff}(t+\Delta t)\varepsilon(t+\Delta t)\right)=0$$

4. Go back to step 1 and change the bone structure. Repeat until convergence is achieved.

Taking into account biological factors in modeling bone adaptation. The theories discussed above take into account the influence of mechanical factors on bone adaptation. Biological factors are no less significant.

The following concept for modeling bone adaptation was developed by Figri and Schaffler in 1995. Figri and Schaffler noted that bone tissue will not be completely destroyed even in the absence of mechanical factors. Previous models predicted complete bone loss if there are no active mechanical forces:

$$\frac{d\rho(t)}{dt}=B(\phi(\sigma,\rho(t))-F).$$

Here B is the reconstruction coefficient, F the target state, ϕ is a function of the target state, which depends on compression and pre-density. Figri and Schaffler proposed that instead of adaptation to mechanical stimuli, use the adaptation of the tissue matrix by bone cells to a certain level of density, which is a function of biological influences and mechanical stimulation. According to this assumption, the equation of evolution of tissue structure should look like this:

$$\frac{d\rho(t)}{dt}=B(\rho(t)-M(E))$$

Here B is a constant reconstruction, M a function that depends on the applied mechanical stimulus, but which is not necessarily zero in its absence.

Algorithms for modeling the adaptation of bone tissue at the cellular level.In all the algorithms proposed above, the work of cells in the process of continuous bone reconstruction was considered a "black box". In 1998, Mulender [93] applied an adaptation algorithm similar to the previous ones at the cell level. The components corresponding to mechanical stimuli were changed and the general function of influences was included. In fact, this influence function is designed to simulate communications through a network of osteocytes. It is assumed that the influence of mechanical stimuli is stronger directly on the osteocyte, but it also affects neighboring osteocytes. Mulender proposed the following type of function of influences:

$$f_i(x) = e^{-\frac{d_i(x)}{D}}.$$

Here d_i is the radius in millimeters from the center of the osteocytes, D is a constant that determines the rate of extinction of the impact. Using the influence function, it is possible to write the following mechanical error function that controls reconstruction at the cellular level:

$$F(x,t) = \sum_{i=1}^{n} f_i(x)\left[S_i(t) - k\right].$$

Here S_i is a mechanical stimulus (Mulender chose it as a tensile energy density), f_i - a function of influences, k - a reconstruction constant (it can be considered as a target level of tensile energy density). The algorithm for tissue reconstruction can be written by the following equation:

$$\frac{dm(t)}{dt} = \tau F(x,t)$$

Here m it is bone mass, F - a function of mechanical errors, τ - a reconstruction constant, which controls the rate of reconstruction. It is assumed that the structural and functional relationship at the cellular level has a similar appearance to those used in the simulation of continuous reconstruction:

$$E(x,t) = Cm^3(x,t).$$

This is E Young's modulus, C which is m the bone mass. Using such modeling to assess osteoporosis, Mulender simulated both changes during exercise and changes in their absence. It was found that a decrease in the constant k leads to bone thinning and vice versa. Changes in load lead to irreversible processes in the bone architecture, which is very important in the study of osteoporotic bone damage. In general, the Mulender algorithm for reconstruction at the cellular level can be written as follows:

1. Change the structure of the bone:

$$\frac{dm(t)}{dt} = \tau F(x,t)$$

2. Change the effective strength of the bone based on the altered bone structure:

$$c^{eff} = f(e(t+\Delta t), C) \Rightarrow E = a\rho^b$$

3. Solve the equation of equilibrium with new strength to determine the new compressive-tensile fields:

$$\frac{\partial}{\partial x}\left(c^{eff}(t+\Delta t)\varepsilon(t+\Delta t)\right) = 0$$

4. Go back to step 1 and change the bone structure. Repeat until convergence is achieved.

2.6. Construction of a model of bone tissue reconstruction based on logistic-type equations

In this subsection, we will consider a method of building a deterministic dynamic model for the study of one important problem of medicine. This algorithm can be used to solve more general problems.

The growing share of primary and secondary osteoporosis [66] in the structure of the general morbidity of the population [128] of different countries of the world [88,96] draws the attention of researchers of various directions to the study of bone tissue reconstruction both among healthy populations and in various types of pathology [65,88].

One of the most common methods for measuring bone mineral density is one- and two-photon X-ray densitometry for the peripheral (radius and heel) and axial (proximal femur and spine) skeleton.

The method of double X-ray absorptiometry was originally implemented on X-ray absorptiometers (DXA - DEXA technology) of LUNAR Corporation, which are based on the principles of comparing data on bone density obtained during the study of a particular patient with a built model of the state of bone density in a separate ethnic population (separately for white, black, Asian races), taking into account the most stable population indicators (age, weight, height, etc.). Such mathematical models, created by step-by-step regression analysis based on large population studies, describe bone density in a particular ethnic group. Thus, the mineral density of bone tissue in the Ward's triangle in the white European population aged 40-65 years is described by the equation:

$$\rho(t) = 1.05 - (0.0045 \cdot t),$$

where t is the age of the patient.

Densitometric examinations of the lumbar spine and femur are carried out in the consultative and therapeutic center of the Ternopil State Medical Academy on the densitometer DPX-A (LUNAR Corp.) [32]. It consists of (Fig. 2.6.1):

- a table for placing a patient with control devices built into its base and a tripod with devices for scanning and focusing the laser beam;

- a computer that manages the scanning process and analyzes the data obtained;

- a monitor on which the obtained research data and a printer are visualized.

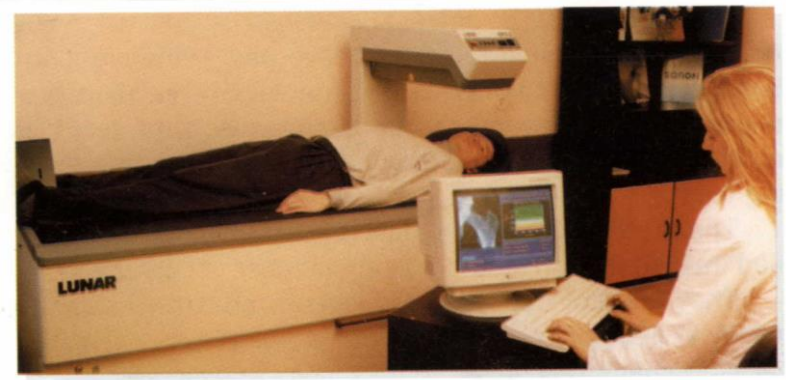


Fig 2.6.1. DPX-A Densitometer (Lunar Corp.)

The scanning table consists directly of a table and a scanning "arm". Power sources, electronic boards, motors with movement mechanisms and an X-ray source are built inside the table. The "arm" of the scanner consists of a scintillation detector and a holder in which the detector's communication cable with the electronic boards of the table pass. The scanning "arm" is equipped with a control panel with two switches to determine the position of the detector. The Back/Front switch allows you to accurately set the detector position across the width of the table; the Left/Right switch allows the detector to move along the length of the

table. The "shoulder" is also equipped with four signal bulbs that induce the position of the damper, the supply of power to the table, the laser and to the X-ray tube. The computer stores and analyzes the results obtained during the scan, it also controls the table. The monitor provides (with the help of specialized software) visualization of research data and images of the scanning region.

With the help of DPX-A, the proximal femur is examined in three areas: the femoral neck (Neck), Wards' triangle (Wards), and the greater trochanter (Trochanter). After scanning the experimental area, which, depending on the scanning mode, takes from 2 to 10 minutes, the results are analyzed by a computer.

The results are displayed on the monitor in the form of a color graph, in numerical and percentage form. The printer prints data in the form of tables.

The purpose of the next study will be to build a mathematical model of the state of bone tissue in patients with pathology of the hematopoietic apparatus. On the absorption X-ray densitometer of the company "Lunar Corp" (USA), the state of bone tissue of the lumbar spine was studied in 300 hematological patients [32].

Approaches to the construction of a mathematical model are based on preliminary statistical assessment of the obtained densitograms and studies [66,88,98]. The model is based on the following assumptions regarding the nature of changes in bone mineral density.

In a fairly short period of time Δt, the rate of change in bone density $\frac{\Delta\rho(t)}{\Delta t}$ proportionally depends:

- on the value of density at a given time t, that is $\rho(t)$, corresponding to the exponential nature of growth $\rho(t)$ with age, inherent in most quantitative indicators of the state of the body;
- from the size $\rho^2(t)$ of .

The latter assumption indicates that a certain limit value has been reached with age ρ^*.

So, for a change $\rho(t)$ A difference equation is proposed

$$\frac{\Delta\rho(t)}{\Delta t} = \alpha\rho(t)\big(\beta - \rho(t)\big), \qquad (2.6.1)$$

that passes into $\Delta t \to 0$ the differential equation

$$\rho'(t) = \alpha\rho(t)\big(\beta - \rho(t)\big). \qquad (2.6.2)$$

Here a and β are the unknown parameters of the model, which must be determined on the basis of experimental data. Note that this model, which does not take into account other indicators of the state of bone tissue, can be used to describe changes $\rho(t)$ at the age of 15-70 years.

Algorithm for finding unknown parameters α, β**.** Analysis of densitometric research data is somewhat difficult for the following reasons:

- a wide range of indicators of the condition due to the peculiarities of the formation of bone tissue in different strata of the population with a certain age;
- the influence of various kinds of diseases on the mineral density of bone tissue;
- the inability to trace the change in the mineral density of the patient's bone tissue, since the process of bone formation takes a long time.

Therefore, the following algorithm for finding unknown parameters is proposed α, β based on research data.

1. Averaging. In this case, on the basis of real indicators of bone mineral density, average values are calculated $\overline{\overline{\rho_n}}$. Here n is the age of patients in years.

$$\overline{\overline{\rho_N}} = \frac{1}{k(N)} \sum_{m=1}^{k(N)} \rho_n^m, \overline{\overline{\rho_n}} = \overline{\overline{\rho_N}}, n = \overline{N-1, N-3}, \overline{\overline{\rho_n}} = \frac{1}{5} \sum_{l=n}^{n+4} \frac{1}{k(l)} \sum_{m=1}^{k(l)} \rho_n^m, n = \overline{N-4, n_0},$$

(2.6.3)

Here n_0, N is the minimum and maximum value of the age of the patients under study $k(l)$ - the number of patients l aged years, ρ_n^m - m the patient of n the age years.

2. Linearization. The proposed difference equation is as follows:

$$\frac{\overline{\overline{\rho_{n+1}}} - \overline{\overline{\rho_{n-1}}}}{2} = \alpha \overline{\overline{\rho_n}} (\beta - \overline{\overline{\rho_n}}), n = \overline{n_o + 1, N-1} \tag{2.6.4}$$

Taking into account $\rho_n \neq 0$ that , we arrive at the equation of linear regression with respect to α and β

$$\frac{\overline{\overline{\rho_{n+1}}} - \overline{\overline{\rho_{n-1}}}}{2\overline{\overline{\rho_n}}} = \alpha\beta - \alpha \overline{\overline{\rho_n}} \tag{2.6.5}$$

3. Solution of the regression equation (2.6.5) with respect to α and β by the method of least squares. We come to the system of equations

$$\alpha\beta \sum_{n=n_o+1}^{N-1} \overline{\overline{\rho_n}} - \alpha \sum_{n=n_o+1}^{N-1} \overline{\overline{\rho_n}}^2 = \sum_{n=n_o-1}^{N-1} \frac{\overline{\overline{\rho_{n+1}}} - \overline{\overline{\rho_{n-1}}}}{2},$$

$$\alpha\beta(N - n_o - 1) - \alpha \sum_{n=n_o+1}^{N-1} \overline{\overline{\rho_n}} = \frac{\overline{\overline{\rho_{n+1}}} - \overline{\overline{\rho_{n-1}}}}{2\overline{\overline{\rho_n}}} \tag{2.6.6}$$

Note: Note that the estimates for the parameters α, β as solutions of equations (2.6.6) are rather inaccurate. The reason is that they are based on a rather

"rough" approximation of the desired differential equation (2.6.2) to the difference equation (2.6.4), where the grid step is one year.

4. Estimates from (2.6.6) are selected as an initial approximation for the parameter identification problem α, β.

Next, to find the parameters α , β we will use the result of theorem 2.6.1.

5. Select the solutions of the system of equations (2.6.6) as initial approximations α_0 and β_0.

6. We check the fulfillment of the conditions for the identification of parameters:

$$\det \int_{t_0}^{T} U_{\mu}^{T}(t,\mu_0)U_{\mu}(t,\mu_0)dt \neq 0, \quad \mu_0 = (\alpha_0,\beta_0).$$

Here $U_{\mu}(t,\mu_0) \in R^2$ is the solution of the differential equation:

$$\begin{cases} \dfrac{dU_{\mu}(t,\mu_0)}{dt} = \big(\alpha\beta - 2\alpha\rho(t,\mu_0)\big)U_{\mu}(t,\mu_0) + \begin{pmatrix} \beta\rho(t,\mu_0) - \rho^2(t,\mu_0) \\ \alpha\rho(t,\mu_0) \end{pmatrix}, \\ U_{\mu}(t_0,\mu_0) = \begin{pmatrix} 0 \\ 0 \end{pmatrix}. \end{cases}$$

If the condition is violated, then the algorithm is terminated. μ_0 - found parameter value.

7. Approximation α_1 and β_1 calculation according to the formulas:

$$\alpha_1 = \alpha_0 + \Delta\alpha_0,$$

$$\beta_1 = \beta_0 + \Delta\beta_0.$$

Here

$$\big(\Delta\alpha_0, \Delta\beta_0\big) = \left(\int_{t_0}^{T} U_{\mu}^{T}(t,\mu_0)U_{\mu}(t,\mu_0)dt \right)^{-1} \int_{t_0}^{T} U_{\mu}^{T}(t,\mu_0)\Big(\overline{\overline{\rho}}(t) - \rho(t,\mu_0)\Big)dt\,.$$

8. We integrate equation (2.6.2) for the values of the parameters $\mu_1 = (\alpha_1,\beta_1)$. The solution is denoted by $\rho(t,\mu_1)$.
9. We return to step 6 and then find the following values $\mu_i = (\alpha_i,\beta_i)$ until convergence is achieved.

2.7. The relationship between mineral bone density and vertebral height

The following assumptions are made. Let in a fairly short period of time Δt the rate of change in BMD $\frac{\Delta\rho(t)}{\Delta t}$:

- proportionally depends on the total height of the vertebrae L1 - L4 $H(t)$;
- proportionally depends on the magnitude $\frac{\rho(t)}{H(t)}$ of .

The last two assumptions indicate the dependence of changes in the BMD on the state of the L1 - L4 vertebrae . It has been established [32] that it is the height of the L1 - L4 vertebrae that significantly affects the aging process of the human body.

Let in a fairly small period of time the Δt rate of change in the total height of the vertebrae L1 - L4 $\frac{\Delta H^{-1}}{\Delta t}$:

- proportionally depends on H^{-1} a given time t;
- proportionally depends on $\rho(t)$.

So, to describe the changes, $\rho(t)$ a H^{-1} system of differential equations is proposed

$$\begin{aligned} \frac{d\rho(t)}{dt} &= \alpha\rho(t) + \nu\rho(t)H^{-1}(t) + \gamma H^{-1}(t), \\ \frac{dH^{-1}(t)}{dt} &= \delta H^{-1}(t) + \mu\rho(t) \end{aligned} \tag{2.7.1}$$

Here $\alpha,\nu,\gamma,\delta,\mu$ are unknown parameters. The algorithm for finding model parameters $\alpha,\nu,\gamma,\delta,\mu$ uses the steps above described algorithm for finding model parameters α,β , namely:

1. Averaging.
2. Smooth.
3. Linearization.
4. Solution of regression equations.

We only note that smoothing and linearization are carried out separately for $\rho(t)$ and $H^{-1}(t)$. The system of equations obtained to determine the initial approximations of the coefficients has the form:

$$\gamma\sum_{n=n_o+1}^{N-1}\left(\frac{\overline{\overline{H^{-1}}}_n}{\overline{\overline{\rho}}_n}\right)^2+\nu\sum_{n=n_0+1}^{N-1}\frac{\left(\overline{\overline{H^{-1}}}_n\right)^2}{\overline{\overline{\rho}}_n}+\alpha\sum_{n=n_0+1}^{N-1}\frac{(\overline{\overline{H^{-1}}}_n)^2}{\overline{\overline{\rho}}_n}=\sum_{n=n_0+1}^{N-1}\frac{\overline{\overline{H^{-1}}}_n(\overline{\overline{\rho}}_{n+1}-\overline{\overline{\rho}}_{n-1})}{2\overline{\overline{\rho}}_n^2},$$

$$\gamma\sum_{n=n_0+1}^{N-1}\frac{(\overline{\overline{H^{-1}}}_n)^2}{\overline{\overline{\rho}}_n}+\nu\sum_{n=n_0+1}^{N-1}(\overline{\overline{H^{-1}}}_n)^2+\alpha\sum_{n=n_0+1}^{N-1}\overline{\overline{H^{-1}}}_n=\sum_{n=n_0+1}^{N-1}\frac{(\overline{\overline{H^{-1}}}_n)^2(\overline{\overline{\rho}}_{n+1}-\overline{\overline{\rho}}_{n-1})}{2\overline{\overline{\rho}}_n^2},$$

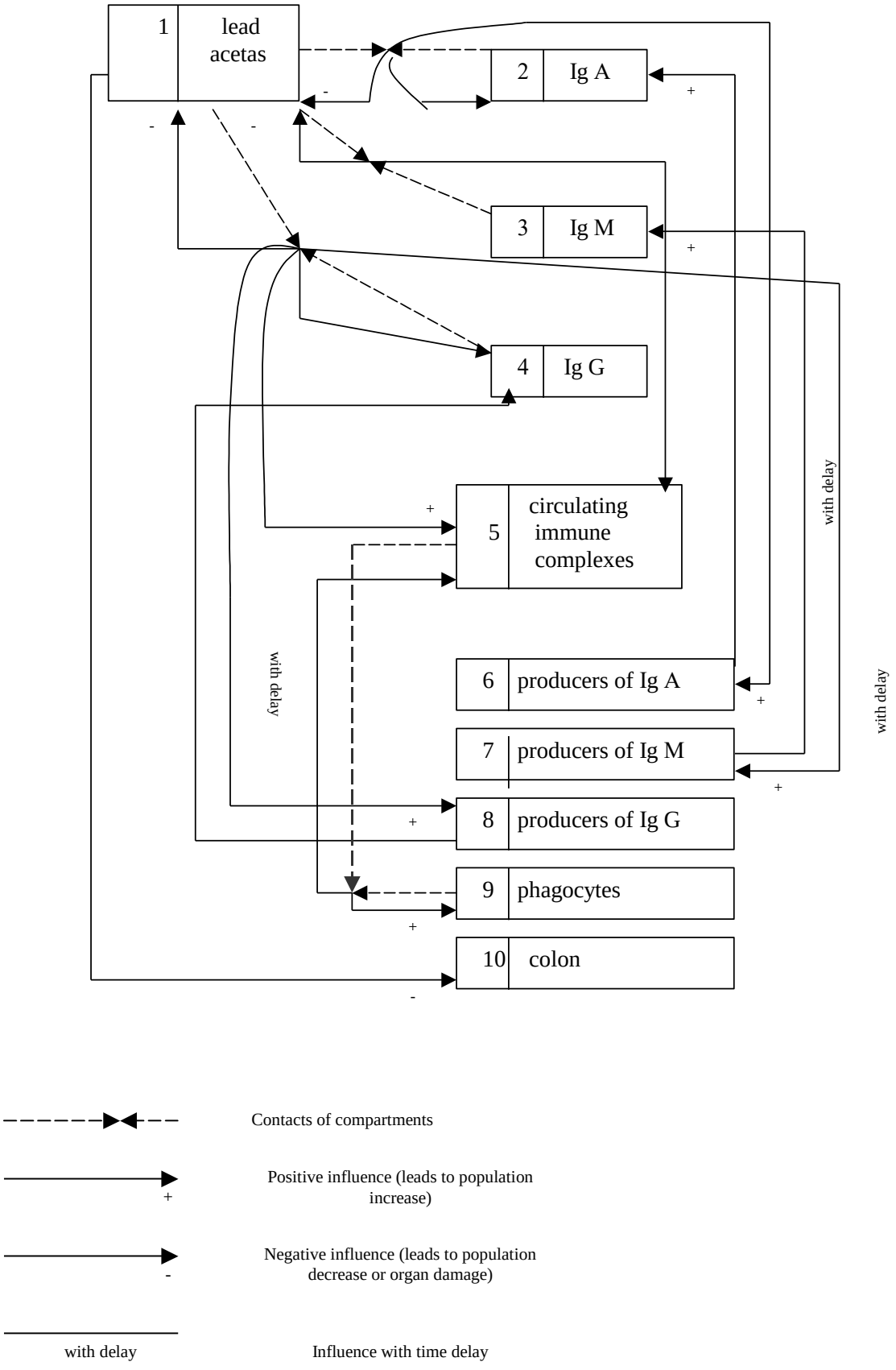
$$\gamma\sum_{n=n_0+1}^{N-1}\frac{\overline{\overline{H^{-1}}}_n}{\overline{\overline{\rho}}_n}+\nu\sum_{n=n_0+1}^{N-1}\overline{\overline{H^{-1}}}_n+\alpha(N-n_0-1)=\sum_{n=n_0+1}^{N-1}\frac{\overline{\overline{\rho}}_{n+1}-\overline{\overline{\rho}}_{n-1}}{2\overline{\overline{\rho}}_n^2},$$

$$\mu\sum_{n=n_o+1}^{N-1}\left(\frac{\overline{\overline{\rho}}_n}{\overline{\overline{H^{-1}}}_n}\right)^2+\delta\sum_{n=n_0+1}^{N-1}\frac{\overline{\overline{\rho}}_n}{\overline{\overline{H^{-1}}}_n}=\sum_{n=n_0+1}^{N-1}\frac{\overline{\overline{\rho}}_n(\overline{\overline{H^{-1}}}_{n+1}-\overline{\overline{H^{-1}}}_{n-1})}{2(\overline{\overline{H^{-1}}}_n)^2},$$

$$\mu\sum_{n=n_0+1}^{N-1}\frac{\overline{\overline{\rho}}_n}{\overline{\overline{H^{-1}}}_n}+\delta(N-n_0-1)=\sum_{n=n_0+1}^{N-1}\frac{\overline{\overline{H^{-1}}}_{n+1}-\overline{\overline{H^{-1}}}_{n-1}}{2(\overline{\overline{H^{-1}}}_n)^2}$$

2.8. Compartment model of experimental toxic colitis based on a nonlinear system with a delay

Today, chronic inflammatory bowel disease is an important medical and social problem due to its wide spread, temporary and long-term disability, as well as severe and complicated course. Among the etiological causes and pathogenetic mechanisms of the development of the disease, the use of low-quality and contaminated food, water, chemicalization of all areas of human life, the difficult environmental situation in general, uncontrolled use of drugs, stress, genetic predisposition, immune, metabolic and microcirculatory disorders, a decrease in the resistance of the gastroduodenal system and the body as a whole are considered [60].



Flowchart 2.8.1. Toxic colitis model

For inflammatory processes of an infectious nature, the decisive factor in terms of the process and its prognosis is the competition of infectious and immune agents. In this regard, the most important are the issues of immunity. Therefore, mathematical models describing the inflammatory process must primarily take into account the body's immune response.

As the phase coordinates of the system, we choose:

x_1 - lead concentration (in mg/1 kg of body weight)

x_2 - concentration of IgA antibodies (in g/l)

x_3 - concentration of IgM antibodies (in g/l)

x_4 - concentration of IgG antibodies (in g/l)

x_5 - indicator of circulating immune complexes (in conventional units)

x_6 - concentration of IgA producing cells (number on the $1мм^2$ intestinal mucosa)

x_7 - concentration of cells - producers of IgM (number on the $1мм^2$ intestinal mucosa)

x_8 - concentration of cells - producers of IgG (number on the $1мм^2$ intestinal mucosa)

x_9 - the number of phagocytic leukocytes (in %)

x_{10} - the degree of damage to the colon.

The colon of 32 male white rats was examined. Toxic colitis was simulated by daily intragastric administration of lead acetate at a daily dose of 50 mg/1 kg of body weight for 3 months [60]. As a unit of time, we will consider 1 day.

Equation for $x_1(t)$.Consider the change $x_1(t)$ over a short period of time Δt. In the case of intragastric administration of lead acetate, which lasts for 30 seconds at a rate $v_1 = 1736100 мг/1 добу$, we have:

$$\Delta x_1(t) = x_1(t+\Delta t) - x_1(t) \approx v_1 \Delta t - k_{1,2} x_1(t) x_2(t) \Delta t - k_{1,3} x_1(t) x_3(t) \Delta t - k_{1,4} x_1(t) x_4(t) \Delta t$$

Here $k_{1,2}$, $k_{1,3}$, are the $k_{1,4}$ coefficients that determine the probability of neutralization of 1 mg of lead acetate by the corresponding antibodies.

In the absence of lead acetate administration from the outside $v_1 = 0$.

Dividing the equation by Δt and directing $\Delta t \to 0$, we get:

$$\frac{dx_1(t)}{dt} = \begin{cases} v_1 - k_{1,2} x_1(t) x_2(t) - k_{1,3} x_1(t) x_3(t) - k_{1,4} x_1(t) x_4(t), t \notin [i, t + 3,472 \cdot 10^{-4}], i = \overline{0,30} \\ -k_{1,2} x_1(t) x_2(t) - k_{1,3} x_1(t) x_3(t) - k_{1,4} x_1(t) x_4(t), t \in [i, t + 3,472 \cdot 10^{-4}], i = \overline{0,30} \end{cases} \quad (2.8.1)$$

Equations for $x_2(t)$, $x_3(t)$, . $x_4(t)$ Let's consider the change $x_2(t)$ within a short period of time Δt. According to block diagram 2.8.1, we have:

$$\Delta x_2(t) = x_2(t+\Delta t) - x_2(t) \approx k_{2,6} x_6(t) \Delta t - k_2 x_2(t) \Delta t - k_{2,1} k_{1,2} x_1(t) x_2(t) \Delta t$$

Here $k_{2,6}$ is the rate of production of IgA antibodies by one plasma cell, k_2 - a coefficient inversely proportional to the decay time of antibodies IgA, $k_{2,1}$ - the number of antibodies required to neutralize 1 mg of lead acetate.

Dividing the equation by Δt and directing $\Delta t \to 0$, we get:

$$\frac{dx_2(t)}{dt} = k_{2,6} x_6(t) - k_2 x_2(t) - k_{2,1} \cdot k_{1,2} x_1(t) x_2(t) \quad (2.8.2)$$

In the same way, we obtain the equation for IgM and IgG:

$$\frac{dx_3(t)}{dt} = k_{3,7} x_7(t) - k_3 x_3(t) - k_{3,1} \cdot k_{1,3} x_1(t) x_3(t) \quad (2.8.3)$$

$$\frac{dx_4(t)}{dt} = k_{4,8} x_8(t) - k_4 x_4(t) - k_{4,1} \cdot k_{1,4} x_1(t) x_4(t) \quad (2.8.4)$$

The introduced coefficients have a similar purpose.

Equation for $x_5(t)$**.** According to the methodology demonstrated above on the example of variables $x_1(t) - x_4(t)$ and in accordance with block diagram 2.8.1, we have:

$$\frac{dx_5(t)}{dt} = k_{5,1,3}x_1(t)x_3(t) + k_{5,1,4}x_1(t)x_4(t) - k_5x_5(t) \qquad (2.8.5)$$

Here k_5 is the coefficient that determines the excretion of circulating immune complexes.

Equations for $x_6(t)$**,** $x_7(t)$**,.** $x_8(t)$

$$\frac{dx_6(t)}{dt} = \xi(x_{10}(t))k_{6,1,2}x_1(t-\tau_6)x_2(t-\tau_6) - k_6(x_6(t) - x_6^0), \qquad (2.8.6)$$

$$\frac{dx_7(t)}{dt} = \xi(x_{10}(t))k_{7,1,3}x_1(t-\tau_7)x_3(t-\tau_7) - k_7(x_7(t) - x_7^0), \qquad (2.8.7)$$

$$\frac{dx_8(t)}{dt} = \xi(x_{10}(t))k_{8,1,4}x_1(t-\tau_8)x_4(t-\tau_8) - k_8(x_8(t) - x_8^0), \qquad (2.8.8)$$

Here $\xi(\cdot): R^1 \to [0,1]$ is a continuous non-increasing function, which characterizes a violation of the normal functioning of the immune system due to significant damage to the colon; $k_{6,1,2}, k_{7,1,3}, k_{8,1,4}$ — coefficients that determine the probability of meeting antibodies with lead acetate particles k_6, k_7, k_8 — coefficients inverse of the lifetime of plasma cells x_6^0, x_7^0, x_8^0 — concentrations of plasma cells in the initial ("healthy") state; τ_6, τ_7, τ_8— the time intervals during which the formation of a cascade of plasma cells is carried out.

Equations for $x_9(t)$

$$\frac{dx_9(t)}{dt} = k_{9,5}x_9(t)x_5(t) - k_9x_9(t) \qquad (2.8.9)$$

Equations for $x_{10}(t)$

$$\frac{dx_{10}(t)}{dt} = k_{10,1}x_1(t) - k_{10}x_{10}(t) \qquad (2.8.10)$$

Here $k_{10,1}$, is a coefficient that determines the rate of cell death due to the damaging effect of lead acetate k_{10} — a coefficient that takes into account the rate of recovery of the damaged organ.

Like the work [51] we put

$$\xi(m) = \begin{cases} 1, & m \le 0.1, \\ (1-m)\dfrac{10}{9}, & 0.1 \le m \le 1. \end{cases}$$

This type of function $\xi(m)$ indicates a slowdown in the process of plasma cell formation when the colon is weakened by toxic colitis.

Identification of parameters based on the quadratic quality criterion. Let $x_з(t) \in R^{10}, t \in [t_0, T]$ be the set values of the indicators of the toxic colitis system at the observation interval $t \in [t_0, T]$. To estimate the parameters of the system (2.8.1)-(2.8.10), we use the consequence 2.4.1. Let's denote $U_\mu(t, \mu, \tau)$ through , $U_\tau(t, \mu, \tau)$ - the sensitivity functions of the system (2.8.1)-(2.8.10). μ

$$\mu = (k_{1,2}, k_{1,3}, k_{1,4}, k_{2,6}, k_2, k_{2,1}, k_{3,7}, k_3, k_{3,1}, k_{4,8}, k_4, k_{4,1},$$
$$k_{5,1,3}, k_{5,1,4}, k_5, k_{6,1,2}, k_6, k_{7,1,3}, k_7, k_{8,1,4}, k_8, k_{9,5}, k_9, k_{10,1}, k_{10})',$$

Under the vector of delays τ

$$\tau = (\tau_6, \tau_7, \tau_8).$$

So, $U_\mu(t,\mu,\tau) \in R^{10\times 25}$, . $U_\tau(t,\mu,\tau) \in R^{10\times 3}$

Sensitivity functions can be found as solutions to the main initial problems:

$$\frac{dU_\mu(t,\mu,\tau)}{dt} = \mathrm{A}U_\mu(t,\mu,\tau) + \mathrm{B}U_\mu(t-\tau_6,\mu,\tau) + \mathrm{E}U_\mu(t-\tau_7,\mu,\tau) + ,$$
$$+\Phi U_\mu(t-\tau_8,\mu,\tau) + \Gamma$$

$$U_\mu(t,\mu,\tau) \equiv \Theta, \qquad t \in \left[t_0 - \max\{\tau_6,\tau_7,\tau_8\}, t_0\right].$$

The following notations are used here for $\mathrm{A} \in R^{10\times 10}$, $\mathrm{B} \in R^{10\times 10}$, $\mathrm{E} \in R^{10\times 10}$, , $\Phi \in R^{10\times 10}$: $\Gamma \in R^{10\times 25}$

$$\mathrm{A} = \begin{bmatrix}
-k_{1,2}x_2 - k_{1,3}x_3 - k_{1,4}x_4 & -k_{1,2}x_1 & -k_{1,3}x_1 & -k_{1,4}x_1 & 0 & 0 & 0 & 0 & 0 & 0 \\
-k_{2,1}k_{1,2}x_2 & -k_2 - k_{2,1}k_{1,2}x_1 & 0 & 0 & 0 & k_{2,6} & 0 & 0 & 0 & 0 \\
-k_{3,1}k_{1,3}x_3 & 0 & -k_3 - k_{3,1}k_{1,3}x_1 & 0 & 0 & 0 & k_{3,7} & 0 & 0 & 0 \\
-k_{4,1}k_{1,4}x_4 & 0 & 0 & -k_4 - k_{4,1}k_{1,4}x_1 & 0 & 0 & 0 & 0 & 0 & 0 \\
k_{5,1,4}x_4 & 0 & k_{5,1,3}x_1 & k_{5,1,4}x_1 & -k_5 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & -k_6 & 0 & 0 & 0 & \begin{cases} 0, x_{10} \le 0.1 \\ -\frac{10}{9}k_{6,1,2}x_1(t-\tau_6)x_2(t-\tau_6), .1 \le x_{10} \le 1 \end{cases} \\
0 & 0 & 0 & 0 & 0 & 0 & -k_7 & 0 & 0 & \begin{cases} 0, x_{10} \le 0.1 \\ -\frac{10}{9}k_{7,1,3}x_1(t-\tau_7)x_3(t-\tau_7), .1 \le x_{10} \le 1 \end{cases} \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & -k_8 & 0 & \begin{cases} 0, x_{10} \le 0.1 \\ -\frac{10}{9}k_{8,1,4}x_1(t-\tau_8)x_4(t-\tau_8), .1 \le x_{10} \le 1 \end{cases} \\
0 & 0 & 0 & 0 & k_{9,5}x_9 & 0 & 0 & 0 & -k_9 - k_{9,5}x_5 & 0 \\
k_{10,1} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -k_{10}
\end{bmatrix}$$

$$B = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ \xi(x_{10})k_{6,1,2}x_2(t-\tau_6) & \xi(x_{10})k_{6,1,2}x_1(t-\tau_6) & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}$$

$$E = \begin{bmatrix} 0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \\ \xi(x_{10})k_{7,1,3}x_3(t-\tau_7) & 0 & \xi(x_{10})k_{7,1,3}x_1(t-\tau_7) \\ 0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix} \Theta$$

$$\Phi = \begin{bmatrix} 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ \xi(x_{10})k_{8,1,4}x_4(t-\tau_8) & 0 & 0 & \xi(x_{10})k_{8,1,4}x_1(t-\tau_8) \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix} \Theta$$

$$\Gamma=\left[\begin{array}{ccccccccccccccc}
-x_1x_2 & -x_1x_3 & -x_1x_4 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0\\
-k_{2,1}x_1x_2 & 0 & 0 & x_6 & -x_2 & -k_{1,2}x_1x_2 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0\\
0 & -k_{3,1}x_1x_3 & 0 & 0 & 0 & 0 & x_7 & -x_3 & -k_{1,4}x_1x_4 & 0 & 0 & 0 & 0 & 0 & 0\\
0 & 0 & -k_{4,1}x_1x_4 & 0 & 0 & 0 & 0 & 0 & 0 & x_8 & -x_4 & -k_{1,4}x_1x_4 & 0 & 0 & 0\\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & x_1x_3 & x_1x_4 & -k_5\\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0\\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0\\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0\\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0\\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0
\end{array}\right.$$

$$\left.\begin{array}{cccccccccc}
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0\\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0\\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0\\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0\\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0\\
\xi(x_{10})x_1(t-\tau_6)x_2(t-\tau_6) & -(x_6-x_6^0) & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0\\
0 & 0 & \xi(x_{10})x_1(t-\tau_7)x_3(t-\tau_7) & -(x_7-x_7^0) & 0 & 0 & 0 & 0 & 0 & 0\\
0 & 0 & 0 & 0 & \xi(x_{10})x_1(t-\tau_8)x_4(t-\tau_8) & -(x_8-x_8^0) & 0 & 0 & 0 & 0\\
0 & 0 & 0 & 0 & 0 & 0 & x_9x_5 & -x_9 & 0 & 0\\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & x_1 & -x_{10}
\end{array}\right]$$

$U_\tau(t,\mu,\tau)$ is the solution of the following problem:

$$\frac{dU_\tau(t,\mu,\tau)}{dt}=\mathrm{A}U_\tau(t,\mu,\tau)+\mathrm{B}U_\tau(t-\tau_6,\mu,\tau)+\mathrm{E}U_\tau(t-\tau_7,\mu,\tau)+\Phi U_\tau(t-\tau_8,\mu,\tau),$$
$$U_\tau(t,\mu,\tau)\equiv\Theta,\qquad t\in\left[t_0-\max\{\tau_6,\tau_7,\tau_8\},t_0\right].$$

To find the parameters μ and values of the delay τ, we will use iterative procedures:

$$\mu_{i+1}=\mu_i+\Delta\mu_i, i=0,1,2,...$$
$$\tau_{i+1}=\tau_i+\Delta\tau_i, i=0,1,2,... \qquad (2.8.11)$$

Here μ_0, τ_0 are the initial approximations of parameters and delays. The values of increments $\Delta\mu_i \in R^{25}$ and $\Delta\tau_i \in R^3$ are calculated according to the formulas:

$$\Delta\mu_i = \left(\int_{t_0}^{T} U_\mu^T(s,\mu_i,\tau_i) U_\mu(s,\mu_i,\tau_i) ds \right)^{-1} \int_{t_0}^{T} U_\mu^T(s,\mu_i,\tau_i) \left(x_э(s) - x(s,\mu_i,\tau_i) \right) ds,$$

$$\Delta\tau_i = \left(\int_{t_0}^{T} U_\tau^T(s,\mu_i,\tau_i) U_\tau(s,\mu_i,\tau_i) ds \right)^{-1} \int_{t_0}^{T} U_\tau^T(s,\mu_i,\tau_i) \left(x_э(s) - x(s,\mu_i,\tau_i) \right) ds,$$

At the same time, we believe that the conditions for the identification of the system are met, namely:

$$\det \int_{t_0}^{T} U_\mu^T(s,\mu_i,\tau_i) U_\mu(s,\mu_i,\tau_i) ds \neq 0, \qquad \det \int_{t_0}^{T} U_\tau^T(s,\mu_i,\tau_i) U_\tau(s,\mu_i,\tau_i) ds \neq 0,$$

$i = 0,1,2...$

Example. Let's use iterative procedures (2.1.11) to numerically find parameters μ and values of delays τ. As initial values, we will choose the values inherent due to the physical content of the parameters:

$$\mu_0 = (0.2, 0.2, 0.2, 0.1, 0.1, 10, 0.1, 0.1, 10, 1, 1, 0.1, 10000, 0.5, 10000, 0.5, 10000, 0.5, 10000, 0.5, 0.01, 1, 300, 0.1)$$

$$\tau_0 = (0.1, 0.1, 0.1)$$

Using the algorithm proposed above, we have:

$$\mu_{10} = (0.23, 0.23, 0.23, 0.17, 0.17, 10, 0.17, 0.17, 10, 0.9, 0.9, 0.1, 10000, 0.5, 10000, 0.5, 10000, 0.5, 10000, 0.5, 0.01, 1, 300, 0.12) \tag{2.8.12}$$

$$\tau_{10} = (0.5, 0.5, 0.5)$$

2.9. An example of the identification of an integral nucleus

A model of the white blood cell population is considered, which plays an extremely important role in the process of hematopoiesis and is an indicator of the toxicity of treatment methods. Since white blood cells originate from the bone marrow [23], they are also associated with bone mineral density [171].

So, let's denote through $x(t)$ the density of white blood cells in the blood (cell units / ml of blood). Based on the results of the study [26], the following equation is proposed:

$$\begin{cases} \dfrac{dx(t)}{dt} = -\delta x(t) + \beta \int_a^b v(s) x(t+s) ds, \quad t \in (t_0, \infty), \\ x(t_0) = x_0, \quad x(t) \equiv 0, \quad t \in (t_0 + a, t_0). \end{cases} \tag{2.9.1}$$

Here $x(t) \in C^1(t_0, \infty)$ is a continuously-differentiable function, $a < b < 0$ (you can consider a case $a = t_0 - t$), x_0 - the initial value is known, $v(s)$ - an unknown integral nucleus. It is assumed that $v(s) \in C^1(-\infty, 0)$ in this case:

$$\begin{cases} \dfrac{dv(s)}{ds} = f_1(s), \quad s \in (a,0), \\ v(a) = v_0 \end{cases} \tag{2.9.2}$$

where $f_1(s) \in L_2(a,0)$, $v_0 \in R$ are the unknown function and initial value.

Let the observation be given:

$$y(t) = x(t) + f_2(t), \quad t \in [t_0, T], \tag{2.9.3}$$

where $f_2(t) \in L_2[t_0, T]$ is the unknown error.

It is necessary to find the estimate of the integral nucleus $v(s)$ if the nucleus itself $f_2(t)$ satisfies the condition with an unknown function:

$$J(f_1, f_2, v_0) = q_1 \int_a^b \left(\frac{dv}{ds} \right)^2 ds + q_2 \int_{t_0}^T f_2^2(t)\, dt + q_0 v_0^2 \le 1. \tag{2.9.4}$$

As an initial approximation of the nucleus $v(s)$, consider the gamma distribution density function:

$$v_0(s) = \begin{cases} 0, \quad s \ge b, \\ \dfrac{\alpha^{m+1}}{\Gamma(m+1)} (b-s)^m e^{-\alpha(b-s)}, \quad s < b, \end{cases} \tag{2.9.5}$$

where $\alpha, m \ge 0$. It has been shown [106]] that such a choice of the density function is in good agreement with experimental data on the time of cell maturation and appears in the modeling of cell cycles [117]. [26] parameter values α, m for people with different types of pathologies] have been calculated.

$$\alpha = 0.36, \quad m = 1.15. \tag{2.9.6}$$

Based on the results of subsection 2.3, the following procedure for identifying the nucleus is proposed $v(s)$.

Algorithm for identifying the integral core $v(s)$ of the problem (2.9.1)-(2.9.4).

1. Enter the parameters of the problem:

-Coefficients $\delta, \beta, q_0, q_1, q_2$;

- initial value x_0;

- the value of moments of time t_0, T, a, b;

- observation $y(t)$, $t \in [t_0, T]$;

- initial approximation $v_0(s)$, $s \in [a, b]$.

2. We are looking for a solution $x_0(t)$ to the problem (2.9.1) at $v(s) = v_0(s)$.

3. We form a cycle starting j from zero, within which:

(1) we are looking for a solution $P(t)$ to the Ricatti equation:

$$\begin{cases} \dfrac{dP(t)}{dt} = -2\delta P(t) + \dfrac{1}{q_1}\displaystyle\int_a^b \int_{t_0}^T x_j(t_1 + s)\,dt_1 x_j(t + s)\,ds - q_2 P^2(t), \\ P(t_0) = 0. \end{cases} \tag{2.9.7}$$

(2) we are looking for a solution to the Cauchy problem:

$$\begin{cases} \dfrac{g(t)}{dt} = -\delta g(t) + P(t) q_2 \left[y(t) - g(t) \right], \\ g(t_0) = x_0 \end{cases} \tag{2.9.8}$$

(3) we look for the solution of the conjugate system:

$$\begin{cases} \dfrac{p(t)}{dt} = \delta p(t) - q_2\left[y(t) - P(t)\, p(t) - g(t) \right], \\ p(T) = 0 \end{cases} \tag{2.9.9}$$

(4) Looking for a score $x(t)$ of:

$$x_{j+1}(t) = P(t)\, p(t) + g(t), \quad t \in [t_0, T] \tag{2.9.10}$$

(5) looking for an integral kernel estimate:

$$v_{j+1}(s) = \frac{1}{q_1} \int_{t_0}^{T} x_j(t+s)\, p(t)\, dt\,. \tag{2.9.11}$$

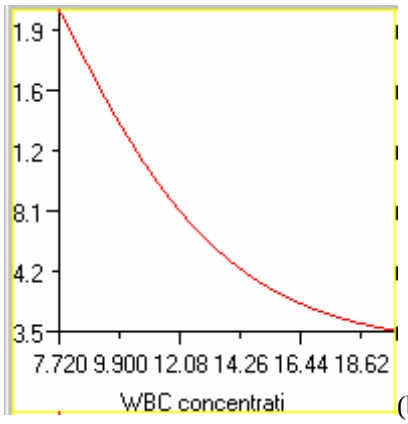
At the same time:

$$v_0 = \frac{1}{q_0}\, p(t_0)\,. \tag{2.9.12}$$

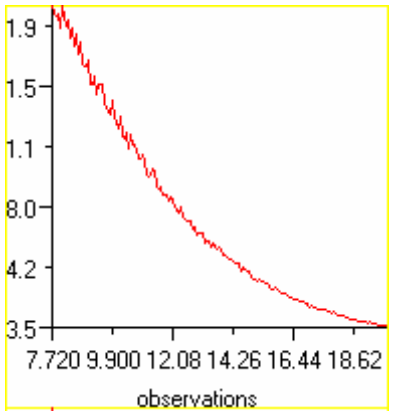
(6) we compare $v(s)$ the values on the two previous iterations: if $\left\| v_{j+1}(s) - v_j(s) \right\| < \varepsilon$, then the end of the algorithm ($v_{j+1}(s)$ is the estimate found), otherwise we go to the beginning of the loop.

Example 2.9.1. On the basis of the algorithm proposed above, a computer program for identifying the integral core of the problem (2.9.1) has been developed. As an initial approximation, the gamma distribution density function (2.9.5) with parameter values (2.9.6) has been selected. The results of its work are shown in Fig. 2.9.1.

(a)


1.9
1.6
1.2
8.1
4.2
3.5
7.720 9.900 12.08 14.26 16.44 18.62
WBC concentrati

(b)


1.9
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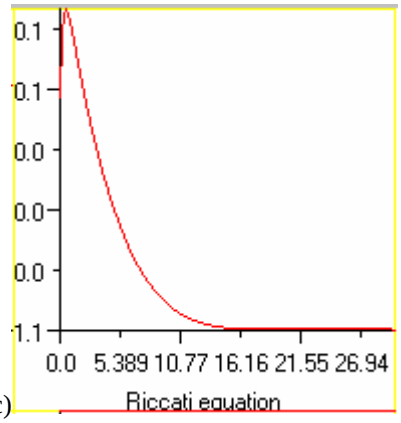
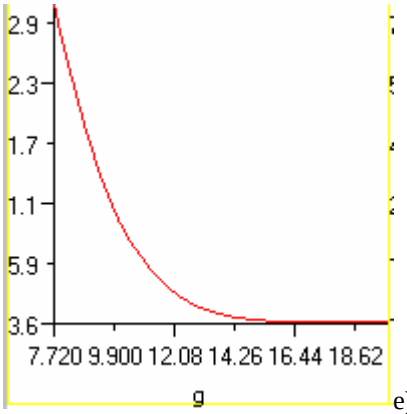
1.1
8.0
4.2
3.5
7.720 9.900 12.08 14.26 16.44 18.62
observations

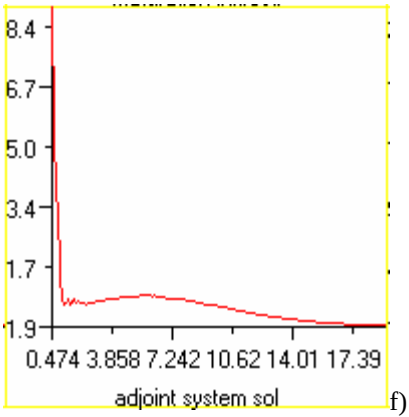
(c)


0.1
0.1
0.0
0.0
0.0
-1.1
0.0 5.389 10.77 16.16 21.55 26.94
Riccati equation

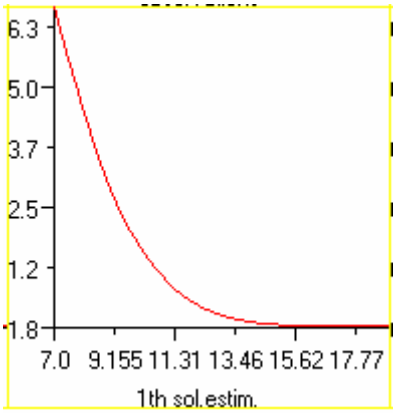
d)

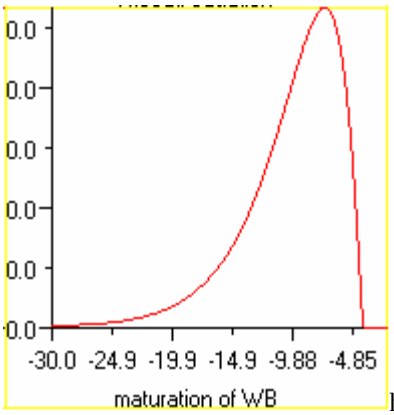

2.9
2.3
1.7
1.1
5.9
3.6
7.720 9.900 12.08 14.26 16.44 18.62
g

e)


8.4
6.7
5.0
3.4
1.7
-1.9
0.474 3.858 7.242 10.62 14.01 17.39
adjoint system sol

f)


6.3
5.0
3.7
2.5
1.2
-1.8
7.0 9.155 11.31 13.46 15.62 17.77
1th sol.estim.

g) 
0.0
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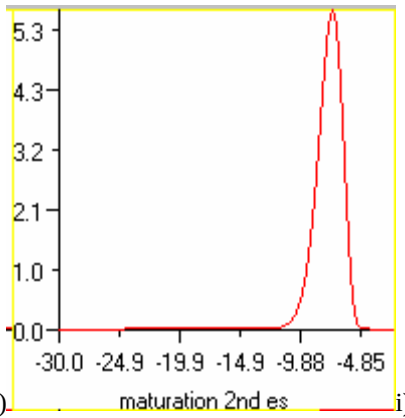
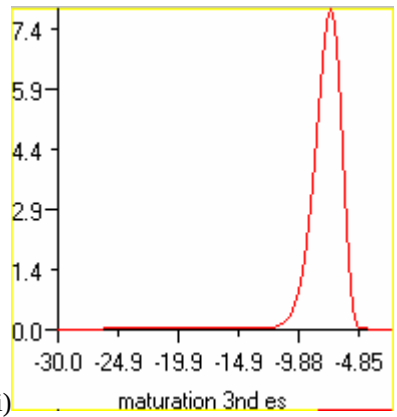
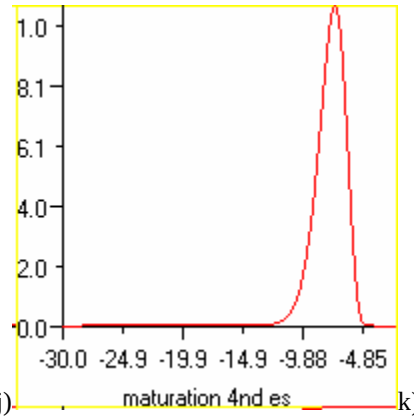
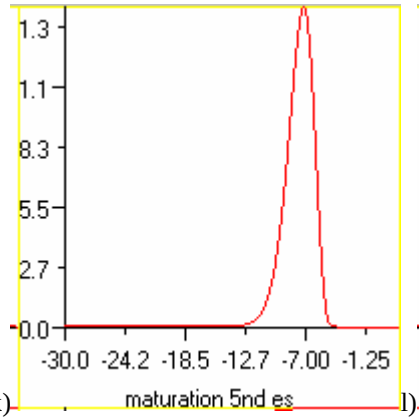
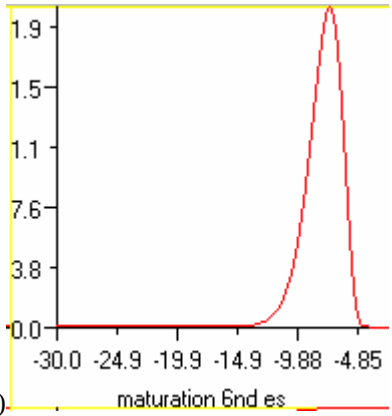
0.0
-30.0 -24.9 -19.9 -14.9 -9.88 -4.85
maturation of WB

h) 
5.3
4.3
3.2
2.1
1.0
0.0
-30.0 -24.9 -19.9 -14.9 -9.88 -4.85
maturation 2nd es

i) 
7.4
5.9
4.4
2.9
1.4
0.0
-30.0 -24.9 -19.9 -14.9 -9.88 -4.85
maturation 3nd es

j) 
1.0
8.1
6.1
4.0
2.0
0.0
-30.0 -24.9 -19.9 -14.9 -9.88 -4.85
maturation 4nd es

k) 
1.3
1.1
8.3
5.5
2.7
0.0
-30.0 -24.2 -18.5 -12.7 -7.00 -1.25
maturation 5nd es

l) 
1.9
1.5
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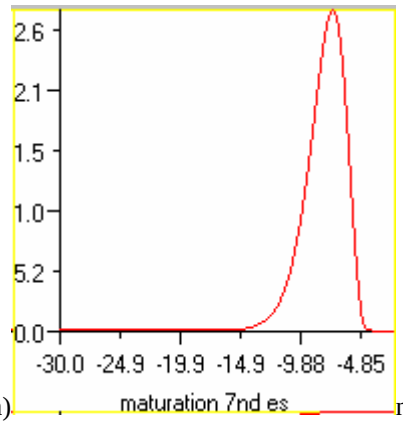
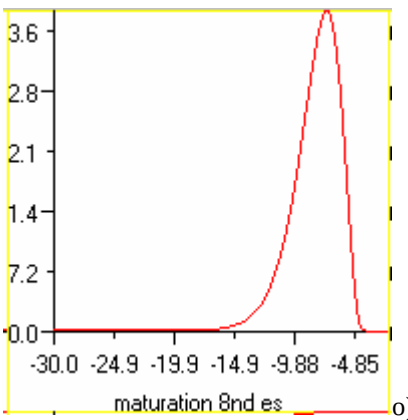
-30.0 -24.9 -19.9 -14.9 -9.88 -4.85
maturation 6nd es

m) 
2.6
2.1
1.5
1.0
5.2
0.0
-30.0 -24.9 -19.9 -14.9 -9.88 -4.85
maturation 7nd es

n) 
3.6
2.8
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1.4
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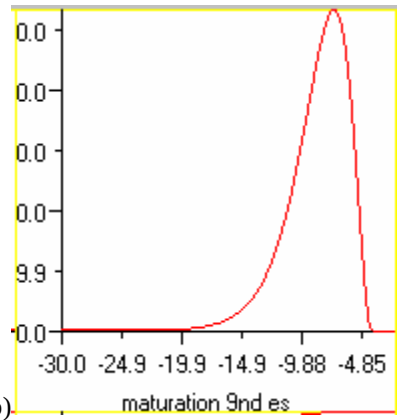
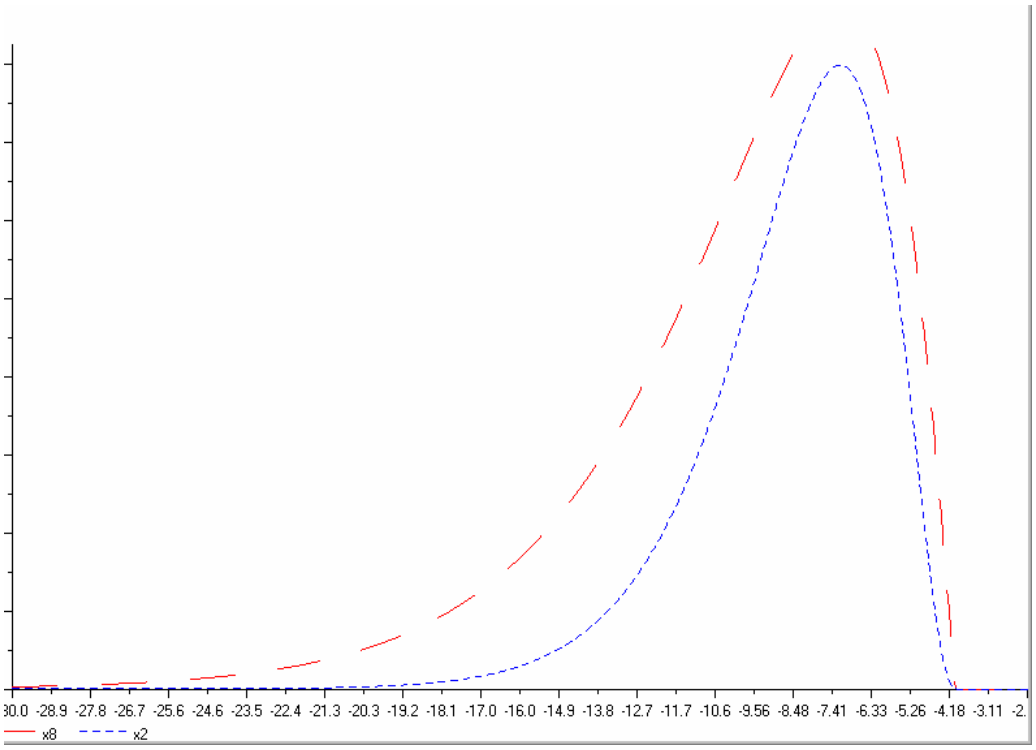
-30.0 -24.9 -19.9 -14.9 -9.88 -4.85
maturation 8nd es

o) 
0.0
0.0
0.0
0.0
9.9
0.0
-30.0 -24.9 -19.9 -14.9 -9.88 -4.85
maturation 9nd es

p) 

Rice. 2.9.1. Results of the program for the system (2.9.1) with parameters

$\delta = 2, \beta = 3.2, q_0 = 1, q_1 = 10^4, q_2 = 0.01, x_0 = 0.001,$
$a = -20, b = -4, t_0 = 0, T = 30$

Here:

a) solving the equation at the initial approximation of the nucleus;

b) observation;

c) the solution of the Ricatti equation;

d) the value of the function g;

e) solution of a conjugate system;

f) an approximate solution has been found;

g) the exact value of the integral nucleus;

h)-o) estimates of the integral core to the 10th iteration.

p) x2 is the exact value of the kernel, x8 is the estimate of the kernel

Conclusions. 1. A solution to the problem of identification of parameters of differential equations given in Hilbert space under conditions of uncertainty has been proposed. The conditions for the existence of solutions of such a problem

have been established, which coincide with the conditions of continuous dependence of solutions of differential equations on parameters. In the case of a linear model and a space, L_2 the condition is a convergence in the standard mean on a priori set. A constructive algorithm for solving the problem of identification in Hilbert space, which is reduced to solving the corresponding boundary value problem. A method of reducing it to Cauchy problems is proposed and one partial case is considered, which allows solving the problem not only in operator form.

2. The estimation problem is solved, when some observations of the system are given, including an unknown integral nucleus, its known state and possibly a derivative. Assuming the differentiation of the integral nucleus and quadratic constraints, a posteriori estimation of the integral nucleus, a posteriori set and an error are obtained. The case of unknown constraints on the initial value of the integral nucleus is also considered. All results were presented in the form that includes solutions of conjugate systems and eigenvalues of some linear operators.

3. Algorithms for solving the problem of estimating the integral nucleus in differential equations with Voltaire operators are constructed. The first approach is to apply an iterative procedure. The second identification algorithm is carried out by decomposition by a small parameter. At the same time, the found estimates are formulated in terms of solutions of conjugate systems. The convergence of the proposed algorithms is shown by a numerical example. Further research should be directed to approbation of the methods proposed in this section for solving the assessment problems presented in [185].

4. An optimization method for identifying parameters in the construction of models of systems with a delay based on sensitivity functions is built and its use for models of pathological processes is demonstrated. Estimates of convergence of this method are obtained.

5. Many methods for identifying the parameters of pathological processes are based on statistical processing of experimental data. Such statistical estimates

of parameters should be chosen as an initial approximation for the proposed optimization procedures for systems with a delay.

6. An overview of the results of solving an important problem of medicine – modeling of bone tissue reconstruction – is presented. A number of numerical algorithms are presented for calculating changes in bone mineral density over time, taking into account both mechanical loads and biological factors. From the above review, it can be seen that modeling changes in bone tissue based on the mineral density indicator makes sense.

7. A model of the process of bone reconstruction in the class of logistic-type equations has been built. Identification of model parameters based on the optimization algorithm is carried out.

8. The method of parameter identification is also illustrated in the construction of a compartment model of the disease, namely, experimental toxic colitis.

These results were reflected in monographs [170, 173, 185], a number of journal articles [158, 175, 176, 180, 190, 192, 194] and conference proceedings [153, 164].