WORKING PAPER

MATHEMATICAL MODELLING AND ANALYSIS OF DATA FROM IMMUNOLOGICAL TESTS FOR ONCOLOGICAL PATIENTS

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Foreword

This paper deals with mathematical modelling and related data processing from immunological tests for oncological patients. A model for describing the dynamics of the observed data is given. A method for investigating mortality dynamics as a function of inspecting clinical indices is suggested. This approach is then used for an analysis of immunological data from patients with stomach cancer.

The results may be useful for estimating the state of the organism during disease and for solving a related optimal control problem. The solution may be interpreted as a recommendation for therapy.

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Mathematical Modelling and Analysis of Data from Immunological Tests for Oncological Patients

A.L. Asachenkov, B.G. Sobolev and E.S. Smolianinov

Introduction

A state of the organism during disease is estimated by means of measurement in clinical tests which can be considered as observed variables of the mathematical model of the process. Functional disturbances to the homeostasis of the organism, which are induced by the disease, reduce to deviations these variables from the values corresponding to the healthy state of the organism. Inspection for the state of the organism during illness which is based on an objective analysis of available information is a useful concept for choosing the method of treatment [5].

An actual problem of clinical oncology is the prediction of individual reaction of a tumor process on the method of treatment. At the present time it is not possible to predict individual sensitivity of the patients to methods of treatment, and to inspect the tumor growth process during treatment using usual statistical methods for processing of the clinical data.

One way to solve this problem consists in construction of an integral index for describing the dynamics of the illness as a function of laboratory measured variables. In this work we investigate the connection between the dynamics of the observed variables and mortality dynamics which is a fundamental development characteristic of tumors [1], [2].

In Section 1 some aspects of oncological illness which are important for mathematical modelling are studied. Here, mortality dynamics, the stochastic character of the dynamic observed variables, heterogeneity population of patients, connection between a mortality index and individual dynamic of the laboratory data are discussed.

In Section 2 a model for describing the dynamics of the observed data is given. The method for investigating mortality dynamics as a function of inspecting clinical indices is suggested.

In Section 3, methods for estimating parameters of these models are discussed.

Then, in Section 4 such an approach is used for analysis on immunological data at the patients with stomach cancer. Experimental data was submitted by E.S. Smolianinov and N.V. Vasiliev from the Tomsk oncological institute.

1. Oncological Disease

Let us discuss some aspects of the oncological disease which are important for mathematical modelling.

a) After surgery the remaining tumor mass can increase and metastatic spreading without expressing clinical symptoms during a long period of months and years. The remaining process of tumor growth acting on the main physiological systems of the organism reduces to its functional disturbances.

In turn the organism, to the development of the neoplastic process, responds by means of physiological and compensating reactions. These reactions provide stability of the basic physiological functions of the organism and guarantee neutralization of infrequent and random disturbances of the homeostatic system. Systematic disturbances in most systems of the organism for a long period of time reduce to considerable structural and functional disturbances [6], [7].

Consequently, the state of the patients at each instant of time can be considered as a point in the space of physiological parameters which are characteristic for functional disturbances of the homeostatic system. And the disease dynamics can be considered as a trajectory in this space.

One of the system ensuring anti-tumor resistence of the organism, as is known, is the immune system. Some immunological indices can be measured in the clinic. We will study disease dynamics from the point of view of variation of such immunological indices.

b) The clinical form of dynamics of oncological illness (aggressive, torpid or slack and unprogressive) is characterized by the life span of the patients after surgery. The life span depends on the activity of disease. The main difference of tumor disease from infectious ones is that the patient's death by infectious disease has more random character with respect to these diseases than, as in the first case, encouraging and morbid forecasts are determined by the anti-tumor resistence of the organism.

Activity of the disease as a rate of the pathological processes can be estimated from measurements of the immunological indices.

If we consider the dynamics of the tumor disease for a group of patients as trajectories in the space of the parameters we can see breaking trajectories. The instants of

break of the trajectories have some stable distribution for the stage of illness, method of treatment, etc.

For example, mortality dynamics have a good correlation with the clinical and morphological estimations of the process (see Fig. 1).

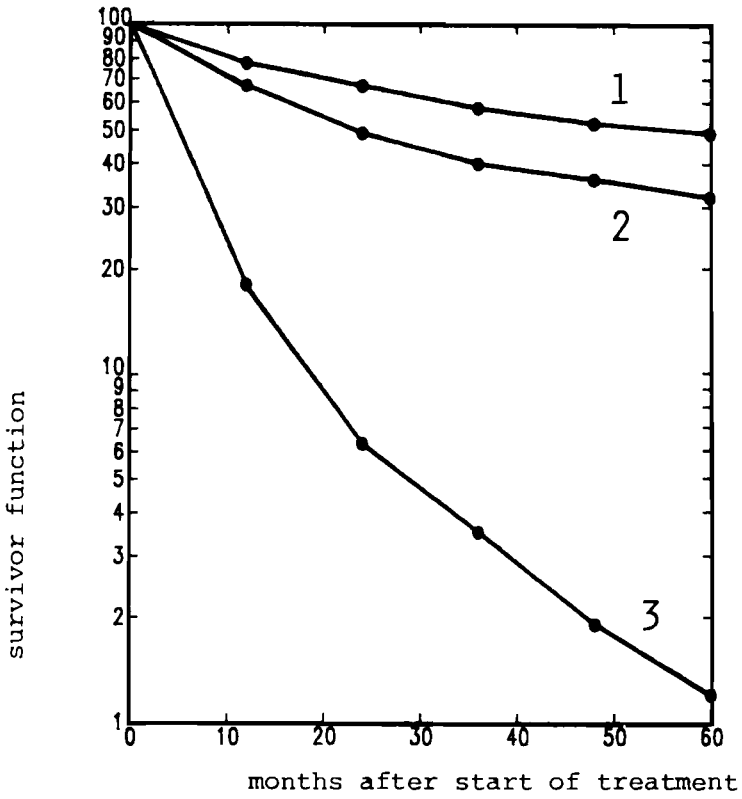


Fig. 1. Example of the mortality dynamics with respect to clinical and morphological estimations of the process. (1 – solid tumor; 2 – local mestastatics; 3 – distant metastatics.)

Consequently, the index for describing the dynamics of illness must be connected with the characteristics of mortality dynamics.

c) It is very difficult to separate a group of tumor patients which have complete functional recovery systems and organs and complete clinical recovery after operative procedures. Nevertheless to study dynamics of disease in the different groups of patients we can compare dynamics of the disease in these groups with dynamics of the patients from the group with the best clinical form of disease in which the life span after the beginning of treatment is maximum. For example 5 years, because after 5 years a character of decreasing in the group of individuals with the same age is equal to the factor of natural death.

Individual life span after the beginning of treatment depends on the rate of tumor process or activity of disease which was investigated by the characteristic deviations of immunological indices for patients with a different form of disease from that in the group with the best clinical form of disease. Then the contribution of these deviations in the mortality dynamics are estimated.

There are many factors which influence the deviations of individual parameters from the trajectory of these parameters in the group of patients with the best clinical form of disease that allows us to consider these deviations in the group of patients as realizations of some stochastic process.

Connection between the basic characteristics of disease can formally be represented in the following form (Fig. 2).

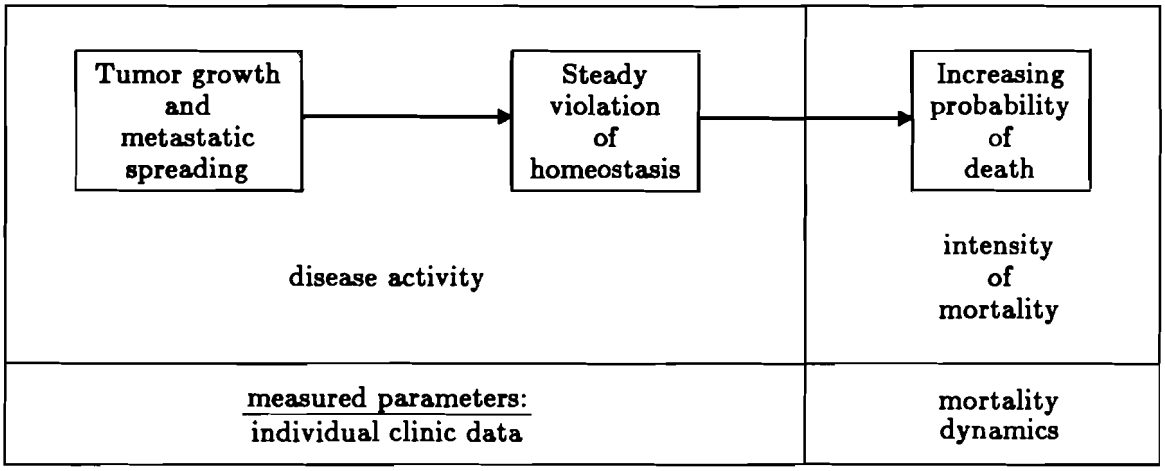


Fig. 2. Principal characteristics of the oncological disease.

From this diagram we can see that the tumor dynamics can be described by means of mortality dynamics and the disease activity. We can observe the mortality dynamics of a group of patients but the activity disease can only be estimated by means of clinically or immunologically measured parameters during illness.

1.2. Survivor Function

Analysis of the processes reduces to patient termination. That allows us to use mathematical methods traditionally used for the study of mortality dynamics. More detailed information can be found in [6], [10].

Denote by $T > 0$ a random variable having a continuous distribution function $F(t) = P\{T \leq t\}$, $t > 0$.

Let T be a patient termination time after the beginning of treatment. Mortality dynamics in group is described by a survivor function

$$S(t) = \int_t^\infty f(u)du, \quad S(0) = 1 , \tag{1.1}$$

where $f(t)$ is a probability density function.

Then the observed group termination intensity or hazard function $\lambda(t)$ is denoted as

$$\lambda(t)dt = P\{t < T \leq t + dt \mid T > t\} . \tag{1.2}$$

Therefore

$$\lambda(t) = - \frac{1}{S(t)} \frac{d}{dt} S(t) = - \frac{d}{dt} \ln S(t) \tag{1.3}$$

or

$$S(t) = \exp \{- \int_0^t \lambda(u)du\} . \tag{1.4}$$

Integral intensity for the interval $[0,t]$ is

$$\Lambda(t) = \int_0^t \lambda(u)du = - \ln S(t), \ \Lambda(0) = 0 . \tag{1.5}$$

We will interpret $\Lambda(t)$ as a load on the organism due to disease at the instant of time t.

Individual dynamics of the disease and intensity of mortality differ from the average observed values in the group and can be considered as random. Consequently, we must study the factors which generate heterogeneity of the population. In the category of such factors we can consider the individual patient dynamics of immunological parameters.

Let $Y(t,\omega) \in R^m$ denote a vector of immunological parameters for the individual with index $\omega \in \Omega$ measured at the instant of time t, where Ω is a set of indices, each element of which characterizes homogeneity with respect to some indicated group of the individuals. Evolution in time $\{Y(t,\omega)\}$ on a set of all patients has a random nature. Then the individual hazard function $\mu(t,\omega)$ must be a random function with respect to $Y(t,\omega)$ and t,

$$\mu(t,\omega) = \mu(Y(t,\omega),t) . \tag{1.6}$$

Individual chances of death in this case are characterized by the conditinal probability

$$P\{T \leq t \mid (Y(u,\omega),\ u \leq t)\} \tag{1.7}$$

or conditional survivor function

$$S(t,\omega) = P\{T>t \mid (Y(u,\omega),\ u \leq t)\} \tag{1.8}$$

where $Y(u,\omega)$, $0 \leq u \leq t$ are individual trajectories of the physiological parameters for those patients with the index ω on the interval of time $[0,t]$. If the conditional survivor function can be represented in the form of

$$S(t,\omega) = \exp\{-\int_0^t \mu(u,\omega)\ du\} \tag{1.9}$$

then the individual hazard function is

$$\mu(t,\omega) = -\frac{d}{dt}\ln S(t,\omega) \tag{1.10}$$

or

$$\mu(t,\omega) = P\{t<T\leq t+dt \mid T\geq t, (Y(u,\omega), 0\leq u\leq t)\}\ .$$

This function indicates the individual intensity of death connected with the tumor process and can be used for analysis of the dynamics of the illness.

Observations in the group mortality dynamics are connected with average intensity of the tumor process for a group of patients. Therefore if the stochastic processes

$$\{Y(t,\omega),\ t\in[0,T],\ \omega\in\Omega\} \text{ and } \mu(Y(t,\omega),t)$$

are denoted, then the observations in group mortality dynamics can be written in the form of

$$P\{T>t\} = E\{\exp\,[-\int_0^t \mu(Y(u,\omega),\ u)\,du]\}\ . \tag{1.11}$$

The following proposition can be made:

Proposition 1. [10]

Let $\{Y(t)\}$ be some H-coordinated stochastic process, and $\mu(Y(t,\omega))$ some positive-definite function such that $\forall_t$

$$E\{\int_0^t \mu(Y(u,\omega))\,du\} < \infty\ . \tag{1.12}$$

Then

$$E\{e^{-\int_0^t \mu(Y(u,\omega))du}\} = e^{-\int_0^t E\{\mu(Y(u,\omega)) \mid T>u\}du}, \tag{1.13}$$

where $T(\omega)$ is a random variable connected with the process $\{Y(t,\omega)\}$ in the following form

$$P\{T>t \mid H_t^Y\} = \exp\{-\int_0^t \mu(Y(u,\omega))du\} .$$

Here

$$H_t^Y = \bigcap_{u>t} \sigma\{Y_v,\ v\leq u\}$$

is σ algebra induced by the trajectories of the stochastic process $Y(u,\omega)$ till the instant of time t when $H = \{H_t^Y\}_{t\geq 0}$. □

Consistent with observations for a group of patients, a convenient hazard function is given by

$$\lambda(t) = -\frac{d}{dt}\ln S(t) = E\{\mu(Y(t,\omega)) \mid T>t\} . \tag{1.15}$$

2. Observable Data. Basis Trajectories

The activity of disease is denoted by a balance between the influence of a tumor on the organism and an immune response on a tumor. Some activity of disease can be estimated from observed data, for example clinically measured immunological indices.

Introduce a new concept -- the best clinical form of disease -- for which the life span after the beginning of treatment is maximum.

Let the dynamics of the clinically measured immunological indices for the group of patients with the best clinical form of disease be described by equation

$$\frac{d}{dt}x(x) = f(x(t),\alpha) ,\ t\in[0,T] , \tag{2.1}$$

$$x(0) = x^0 ,$$

where

$x(t)\in R^m$ is a vector of observable variables ;
$\alpha\in R^l$ is a vector of coefficience .

The vector function $f(x(t),\alpha)$ denoted by the analysis of clinically measured data, as a rule, has the following form

$$f_i(x,\alpha) = \alpha^i + \sum_j \alpha_{ij} x_j + \sum_{j,k} \alpha_{ijk} x_j x_k \,,$$

$$i = 1,\ldots,m,\ \ j = 1,..,m\ ,\ \ k = 1,\ldots,m\ .$$

Denote $\bar{x}(t) = \bar{x}_t = x(t,\alpha_0)$ a solution of the equation (2.1) under $\alpha = \alpha_0$. This solution corresponds to the average dynamics of the observed data for the group of patients with the best clinical form of disease. The solution $x(t,\alpha_0)$ is basis or non-perturbed solution.

2.1. Stochastic model for the deviation from the basis solution

Trajectory deviations of the observed data from the basis solution for patients are due to the influence on the process of uncontrollable clinical factors. The main role is played by a remainder process of the tumor growth and metasthasis. The mathematical model for describing such deviations will consist of ordinary differential equations with random perturbance in the coefficients. Any pathological process developed on the same physiological foundation as a rule are assumed normal, and differ from normal processes only by conditions in the frame of which this process develops. Consequently, the dynamics of the observable data in the normal and pathological conditions can be described by means of the equations with the same structure, and the difference in dynamics is explained by the difference between coefficients of the model.

Let the main source of perturbations be small random deviations of the coefficients α from α_0, due to individual singularity of the organism, i.e., $\delta\alpha = \alpha - \alpha_0$. Consequently, for a group of patients, α is a random vector with the following form

$$\alpha = \alpha_0(1 + \varepsilon'\delta\alpha)\ ,$$

where

$$E\delta\alpha = 0\ ,$$

$$\varepsilon > 0 \ \text{ is a small parameter}\ .$$

On the other hand, the source of the perturbations can be continuous perturbations of the coefficients of the model by stochastic processes which reflect nonregular diffusion influence of difference factors on the organism processes.

Assume that for each trajectory $\{x_t(\omega)\ ,\ \omega\in\Omega\ ,\ t\in[0,T]\}$ there exists a function $\alpha_t(\omega) = \alpha_0 + \xi_t(\omega)$, where $\xi_t(\omega)$ is a fast non-regular perturbation.

Once more the source of the perturbations may be a random deviation of the state variables at the instants of time $t = 0$; for example $x_0 \sim \mathcal{N}(m_0,\gamma_0)$.

In this case, the trajectories of the observed variables can be considered as realizations of some stochastic process which satisfies the equation

$$\frac{d}{dt}x_t = f(x_t,\ \alpha_0 + \varepsilon\xi_t)\ ,\ \ t\in[0,T]\ , \tag{2.2}$$

$$x(0) = q\ \ \text{or}\ \ x(0) \sim \mathcal{N}(m_0,\gamma_0)$$

or

$$\frac{d}{dt}x_t = f(x_t,\ \alpha_0(1 + \varepsilon_1\delta\alpha) + \varepsilon_2\xi_t)\ ,\ t\in[0,T]\ ,$$

$$x(0) = q\ \ \text{or}\ \ x(0) \sim \mathcal{N}(m_0,\gamma_0)$$

where the random variables $\delta\alpha$ and the random process ξ_t are small.

As a rule the fluctuations of the coefficients of the model are due to the influence on the process of numerous factors. According to the central limit theorem [9] it is reasonable to assume that if these factors occur according to distribution functions, if the effect from this influence is small and if these factors are independent then $\delta\alpha$ and ξ_t have Gaussian distributions. Consequently, to construct a model for deviation of the coefficients we don't have to know the mechanism of deviations in detail. Therefore, we assume Gaussian processes for modelling the fluctuations of the model parameters.

Proposition 2. [8]

Let $x_t\in R^m$ satisfy the system equations

$$\frac{d}{dt}x_t = f(x_t,\alpha_0 + \varepsilon\xi_t)\ ,\ \ t\in[0,T]\ , \tag{2.3}$$

$$x(0) = q\ ,$$

where

ξ_t is a stochastic process in R^ℓ,

$\varepsilon>0$ is a small parameter.

Assume that any trajectories of this process are continuous, and that the function $f(x,\alpha)$ has $k+1$ bounded derivatives with respect to x and α. Then, an approximate of the equation (2.3) can be written in the form

$$x_t = x_t^{(0)} + \varepsilon x_t^{(1)} + \cdots + \varepsilon^k x_t^{(k)} + Q_{k+1}(t) ,$$

where the functions $x_t^{(0)}$, $x_t^{(1)}$,... are solutions of the equations

$$\frac{d}{dt}x_t^{(0)} = f(x_t^{(0)}, \alpha_0) , \quad x_0^{(0)} = q , \tag{2.4}$$

$$\frac{d}{dt}x_t^{(1)} = \frac{\partial}{\partial x}f(x_t^{(0)}, \alpha_0)x_t^{(1)} + \frac{\partial}{\partial \alpha}f(x_t^{(0)}, \alpha_0)\xi_t, \quad x_0^{(1)} = 0 ,$$

An estimate of the remainder term is given by

$$\sup_{0\le t\le T} | \, Q_k(t) \, | < c(\omega)\varepsilon^k ,$$

$$P\{c(\omega) < \infty\} = 1 . \quad \square$$

If the model has a form [12]

$$\frac{d}{dt}x_t^\varepsilon = f(x_t^\varepsilon, \alpha_0 + \sqrt{\varepsilon}\,\frac{d}{dt}w_t^\varepsilon) , \quad t\in[0,T] , \quad x_0^\varepsilon = q , \tag{2.5}$$

where

$$w_t^\varepsilon = \frac{1}{\sqrt{\varepsilon}}\int_0^t \xi_{s/\varepsilon} ds ,$$

and ξ_t changing the period of time more less than period of changing of the observable variables and one satisfy the condition of strong intermixing, that is dependence between $\xi_{t+\tau}$, ξ_τ decreases with the growth of τ, then the solution of the equation (2.5) we can write in the form

$$x_t^\varepsilon = x_t^{(0)} + \sqrt{\varepsilon}x_t^{(1)} + \cdots , \tag{2.6}$$

where $x_t^{(1)}$ satisfies the stochastic differential

$$dx_t^{(1)} = \frac{\partial}{\partial x}f(x_t^{(0)},\alpha_0)x_t^{(1)}dt + \frac{\partial}{\partial \alpha}f(x_t^{(0)},\alpha_0)dw_t^\varepsilon \tag{2.7}$$

and consequently

$$\delta X_t^\varepsilon \equiv Y_t^\varepsilon = x_t^\varepsilon - x_t^{(0)} \approx \sqrt{\varepsilon}x_t^{(1)} , \tag{2.8}$$

may be approximated by the equation

$$dY_t^\varepsilon = \frac{\partial}{\partial x} f(x_t^{(0)},\alpha_0)\, Y_t^\varepsilon dt + \frac{\partial}{\partial \alpha} f(x_t^{(0)},\, \alpha_0) dw_t^\varepsilon \,. \tag{2.9}$$

When $\varepsilon \to 0$ the process w_t^ε is weakly convergent to a Gaussian process w_t on the interval $[0,T]$ with $Ew_t = 0$. Here, w_t is an independent - increment process and the covariance matrix Gt[8], where

$$\|G^{ij}\|_{\ell\times\ell},\;\; G^{ij} = \lim_{T\to\infty} \int_0^T \int_0^T E\{\xi_t^i \xi_s^j\}\, dtds \,.$$

In this case, the dynamics of the random deviations $Y_t = x_t - x_t^{(0)}$ is approximated by the linear stochastic differential

$$dY_t = \frac{\partial}{\partial x} f(x_t^0,\, \alpha_0)\, Y_t dt + \Gamma \frac{\partial}{\partial \alpha} f(x_t^{(0)},\alpha_0) dw_t \,, \tag{2.10}$$

$$Y_0 = 0,\;\; t\in[0,T],\;\; \Gamma = \varepsilon G \,.$$

If the intensity of deviations is small then the individual trajectory is not strong and can be withdrawn from the average trajectory $x_t^{(0)}$ on the finite interval of time $[0,T]$, and the difference between these trajectories has random character. If the intensity of deviations increases, variance of the deviations increases since

$$Y_t = \int_0^t H(t,s) \frac{\partial}{\partial \alpha} f(x_s^{(0)},\alpha_0) dw_s \,, \tag{2.11}$$

where $H(t,s)$ is a Green matrix for

$$\frac{d}{dt} Y_t = \frac{\partial}{\partial x} f(x_t^{(0)},\alpha_0)\, Y_t,\;\; Y_0 = 0,$$

and

$$E\{Y_t\} = 0, \tag{2.12}$$

$$E\{Y_t^2\} = \langle \Gamma,\, \int_0^t [H(t,s) \frac{\partial}{\partial \alpha} f(x_s^{(0)},\alpha_0)]^2 ds \rangle \,,$$

where $\langle , \rangle$ is an inner product.

If we have a small systematic deviations vector of coefficients α from the basic values α_0, the equation for deviations can be shown to have the following form for all $\delta\alpha$:

$$dY_t = \left(\frac{\partial}{\partial \alpha} f(x_t^{(0)},\alpha_0)\delta\alpha + \frac{\partial}{\partial x} f(x_t^{(0)},\alpha_0)\, Y_t \right) dt + \Gamma \frac{\partial}{\partial \alpha} f(x_t^{(0)},\, \alpha_0) dw_t \,.$$

2.2. Parametrization of the individual hazard function

The influence of a tumor process on the organism is given by the deviation of physiological parameters from the basis trajectory. Analysis of the observed data shows that the character of deviations of parameters from values which typify the best clinical form of disease, have a good correlation with mortality dynamics or more exactly with life span after the beginning of treatment. In Table 1 the square deviations of the immunological data in the different groups of patients are reduced. It is important that

$$\sigma_a^2 > \sigma_b^2 > \sigma_c^2$$

for all immunological data from Table 1. Using this fact we can parameterize an individual hazard function of the form

$$\mu(Y_t,Q) = Y_t^T Q Y_t \,, \tag{2.14}$$

or

$$\mu(Y_t,Q) = Y_t^T Q Y_t + \lambda_0(t) \,,$$

where

Q – is an unknown symmetrical nonnegative definite matrix of appropriate dimension;

$\lambda_0(t)$ – is a hazard function which is nonconnected with the tumor process.

Table 1. Average square of deviations in various groups of patients.

	Life span after surgery		
Index	a < 12 months	b < 36 months	c > 36 months
B-cells	7.54 (75)	4.60 (389)	0.36 (62)
T-cells % B-cells %	6.86 (75)	3.24 (389)	0.19 (60)
Ig G	3.70 (75)	2.71 (356)	0.12 (75)
Ig A *Ig M*	6.36 (75)	1.50 (356)	0.07 (25)
lim %	1 (74)	0.6 (388)	0.1 (54)

(·) is a number of patients in group

Experimental data from Tomsk Oncological Institute, USSR

2.3. Connection of mortality dynamics with dynamics of immunological data

Assume that the model of the immunological dynamic variables for the best clinical form of disease is known. The equations for deviation, in this case, are chosen in the following form

$$dY_t = (a_0(t) + a_1(t)\,Y_t)dt + \Gamma b(t)dw_t \tag{2.15}$$

$$Y_0 \sim \mathcal{N}(m_0,\gamma_0)\ ,$$

where

$Y_t = x_t - x_t^{(0)} \in R^m$,

$a_0(t)$, $a_1(t)$, $b(t)$ – are known functions appropriate dimensions.

If the hazard function has a form $\mu_t = Y_t^T Q Y_t$, we can construct a system of differential equations which connect mortality dynamics with the deviations of immunological data from basis trajectories.

Proposition 3. [10]

Let a stochastic process

$$\{Y_t(\omega)\in R^m,\ t\geq 0,\ \omega\in\Omega\}$$

satisfy the linear stochastic equation

$$dY_t = (a_0(t) + a_1(t)\,Y_t)dt + \Gamma b(t)dw_t\ ,$$

$$Y_0 \sim \mathcal{N}(m_0,\gamma_0)$$

and conditional survival function has a form

$$s(t,\omega) = \exp\{-\int_0^t Y_u^T Q Y_u du\}$$

where

Q – is a symmetrical nonnegative definite matrix of appropriate dimension.

Then the mortality dynamics for a group of patients is described by a system of ordinary differential equations

$$\frac{d}{dt}\Lambda_t = m_t^T Q m_t + Sp[Q\gamma_t],\ \ \Lambda_0 = 0\ ,$$

$$\frac{d}{dt}m_t = a_0(t) + a_1(t)m_t - 2\gamma_t Q m_t,\ \ m_0 = m_0\ , \tag{2.16}$$

$$\frac{d}{dt}\gamma_t = a_1(t)\gamma_t + \gamma_t a_1^T(t) + \Gamma^T b(t) b^T(t)\Gamma - 2\gamma_t Q\gamma_t\,, \quad \gamma_0 = \gamma_0\,,$$

where

$$\Lambda_t = -\ln S(t)\,,$$

$$m_t = E\{Y_t \mid T>t\}\,,$$

$$\gamma_t = E\{(Y_t - m_t)^T \mid T>t\} \quad \square$$

The proof of this proposition is given in [10]. Therefore, the observable intensity of mortality connects with the dynamics of clinically measured variables of the form

$$\lambda(t) = m_t^T Q m_t + Sp[Q\gamma_t]\,. \tag{2.17}$$

3. Estimating the coefficients of the model

Let us estimate matrices Q,Γ by individual deviations of immunological parameters and observable function $\lambda(t)$.

Functions $a_0(t)$, $a_1(t)$, $b(t)$ are known.

3.1. Statistical estimation by a patient termination time

We can define a probability density function $f(t)$ using known functions

$$\lambda(t) = m_t^T Q m_t + Sp[Q\gamma_t]\,. \tag{3.1}$$

Here

$$P\{T>t\} = \exp\{-\int_0^t \lambda(u)\,du\} \tag{3.2}$$

and

$$F(t) = 1 - P\{T>t\}$$

then

$$f(t) = -\frac{d}{dt}P\{T>t\} = \lambda(t)\exp\{-\int_0^t \lambda(u)\,du\} = \lambda(t)\exp\{-\Lambda(t)\}\,, \tag{3.3}$$

$$\Lambda(t) = \int_0^t \lambda(u)\,du\,,\ \Lambda(0) = 0\,.$$

Let $\beta = (Q,\Gamma)$ be an unknown vector. Then

$$f(t;\beta) = \lambda(t;\beta) \exp\{-\Lambda(t,\beta)\} \tag{3.4}$$

and the likelihood function is

$$\varphi(\beta) = \log p(\theta;\beta) \tag{3.5}$$

where

$$p(\theta;\beta) = \prod_{t\in\theta} f(t;\beta) \ . \tag{3.6}$$

In our case

$$\varphi(\beta) = \sum_{t\in\theta} \log \lambda(t,\beta) - \Lambda(t,\beta) \ , \tag{3.7}$$

and the functions $m_t(Q)$, $\gamma_t(\Gamma,Q)$, $\Lambda_t(Q)$ are defined in (2.16). An estimate of the unknown vector $\hat{\beta}$ is given by

$$\hat{\beta} = \arg\max_{\beta} \varphi(\beta) \ . \tag{3.8}$$

The difficulty of this estimation procedure consists of the following functions m_t, γ_t, Λ_t is the function of Q.

3.2. Estimation by means of a joint equation

In [4, 3, 12] methods for the estimation of coefficients of the system of O.D.E.

$$\frac{d}{dt}x_t = f(x_t,\alpha) \ , \ \ t\in[0,T] \ , \tag{3.9}$$

are discussed. Here $x_t\in R^n$, $\alpha\in R^\ell$, $f(x_t,\alpha) = F(x_t)\alpha$.

The data have the form

$$X_M = \{\hat{x}_t^j\in R^n,\ t\in\Theta,\ j = 1,\ldots,M\} \tag{3.10}$$

$$\Theta = \{t_k : 0<t_1<t_2<\cdots<t_N<T\}$$

3.2.1. Deterministic case

Let $\alpha = \alpha_0 + \delta\alpha$ be an unknown vector of coefficients. If x_0 is known, then the problem of estimating a parameter α leads to that of estimating variations $\delta\alpha$ from $\delta x_t = \hat{x}_t - x(t,\alpha_0)$.

Let us consider the case when $\delta\alpha = \text{const}$ [4 , 3] and in the frame of a given accuracy

$$\hat{x}_t \simeq x(t,\alpha_0 + \delta\alpha) , \quad \forall_t \in \theta .$$

Write the perturbation solution of the system (3.9) $x(t,\alpha_0 + \delta\alpha)$ in power of the small parameter. Using methods from [3] write

$$\delta x_t^i = - \int_0^t \sum_{j=1}^{\ell} \delta\alpha_j \sum_{r=1}^{n} b_{rj} y_{rk}^i(t)\,dt = - \langle \delta\alpha, \psi_k^i \rangle , \tag{3.11}$$

where

$$\psi_k^{ij} = \int_0^T \sum_{r=1}^{n} b_{rj} y_{rk}^i(t)\,dt ,$$

$$b_{rj} = \frac{\partial}{\partial \alpha_j} f_r(x(t,\alpha_0), \alpha_0) ,$$

$$r = 1,\ldots,n, \;\; j = 1,\ldots,\ell .$$

Let $A = \dfrac{\partial}{\partial x} f(x(t,\alpha_0),\alpha_0)$ be an $n \times n$ matrix, and $y_k^i(t) = (y_{1k}^i(t),\ldots,y_{nk}^i(t))^T$ is a vector function on $[0,T]$ which satisfies the system

$$-\frac{d}{dt} y_k^i = A^T y_k^i - p_{jk}^i(t) , \;\; t \in [0,T] , \tag{3.12}$$

$$p_{jk}^i(t) = \begin{cases} 0 & \text{if } j \neq k \\ \delta(t-t_k) & \text{if } j = k , \end{cases}$$

$$k = 1,\ldots,n, \; t_k \in \Theta .$$

where $\delta(t-t_k)$ is the Dirac delta function. In this case $\delta\alpha$ is the solution of the system (3.11). In [12] the iterative method

$$\delta x_{ik}^i(\alpha^u) = - \langle \delta\alpha, \psi_k^i(\alpha^u) \rangle \tag{3.13}$$

$$\alpha^{u+1} = \alpha^u + \delta\alpha^u , \;\; u = 0,1,2,...$$

is discussed. This method is actually the celebrated Newton method such as

$$\alpha^{u+1} = \alpha^u + [\frac{\partial}{\partial\alpha}\phi(\alpha^u)]^{-1}\phi(\alpha^u) ,$$

where

$$\phi(\alpha) = [\varphi_1(\alpha),\cdots,\varphi_n(\alpha)] ,$$

$$\varphi_k(\alpha) = \begin{bmatrix} \hat{x}_{tk}^1 - x_1(t_k,\alpha) \\ \cdots \\ \hat{x}_{tk}^n - x_n(t_k,\alpha) \end{bmatrix}, \quad k = 1,\ldots,n .$$

Convergence of the estimation is given by

$$\|\alpha^u - \alpha^*\| < c^{-1}(c\|\alpha_0 - \alpha^*\|)^{2u} , \quad c<\infty .$$

3.2.2. Stochastic case

The real trajectories of state variables of the model presumably have stochastic character and can not be described in the framework of a deterministic model. The stochastic character of the trajectories depends not only on errors of measurements but also on various internal and external factors which influence the process dynamics. The stochastic character of real trajectories can be taken into consideration by introducing a random perturbation into the model parameters. In this case $\alpha(t) = \alpha_0 + \delta\alpha + \varepsilon\xi_t$ is the function of time, where $\{\xi_t,\ t\in[0,T]\}$ is a stochastic process with $E\xi_t = 0$ and $\varepsilon>0$ is a small parameter. A vector of deviations $\delta x_t(\alpha)$ has random character so that

$$\delta x_{t_k}^i(\alpha) = -\langle\delta\alpha,\ \psi_k^i(\alpha)\rangle + \int_0^T \langle By_k^i,\ dw_s\rangle \tag{3.14}$$

which has approximated a Gaussian probability density function. If the perturbations are independent, the mathematical expectation and dispersion have forms of

$$E\delta x_t^i(\alpha) = -\langle\delta\alpha,\ \psi_k^i(\alpha)\rangle , \tag{3.15}$$

$$D\delta x_t^i(\alpha) = \langle\Gamma,\int_0^T [By_k^i]^2 ds\rangle = \langle\Gamma,\ b^i(t,\alpha)\rangle ,$$

where Γ is a vector of intensity of perturbation. Estimation of the coefficients of the model can be obtained from the likelihood function

$$\phi(\alpha,\delta\alpha,\Gamma) = \sum_{t\in\theta}\sum_i \left\{\ln\langle\Gamma,\ b^i(t,\alpha)\rangle + \frac{[\delta x_t(\alpha) + \langle\delta\alpha;\psi_t^i(\alpha)\rangle]^2}{\langle\Gamma,\ b^i(t,\alpha)\rangle}\right\} \tag{3.16}$$

In [12] it is proven, that the iterative process

$$(\delta\alpha^u, \Gamma^u) = \arg\min_{\delta\alpha,\ \Gamma} \phi(\alpha^u, \delta\alpha, \Gamma) ,$$

$$\alpha^{u+1} = \alpha^u + \delta\alpha^u ,$$

$$\Gamma^{u+1} = \Gamma^u, \quad u = 0,1,2,\cdots$$

is a quasi-Newton process with first-order convergence. The estimations, computed by this method, with probability one, converge to the true values α^*, Γ^* when $N \to \infty$.

4. Example. Analysis of immunological data of patients with stomach cancer

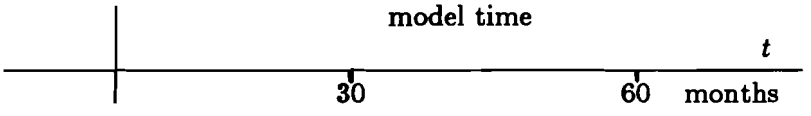
In this section, our approach is used for the analysis of immunological data of patients with stomach cancer. Experimental data was given by N.V. Vasiliev and E.S. Smolianinov from the Tomsk oncological institute. We study the dynamics of the tumor process and oncological patients life span after start of the therapy.

4.1. Preprocessing of clinical data

The immunological data have a large variability between neighboring instants of measurements. This circumstance leads us to preprocessing of the available data. In Table 2 time measured immunological data are given for two methods of treatment.

Table 2. Time measured immunological data for two methods of treatment in months.

Method	Beg. treatment	1 treatment	Surgery	Before and after n courses of treatment									
				n=1	n=2	n=3	n=4	n=5	n=6	n=7	n=8	n=9	n=10
chemotherapy + surgery	0	0.5	1.5	–	–	3.5	5.0	7.5	10.0	12.5	16.0	19.5	23.0
					2.5	4.0	5.5	8.0	10.5	13.0	16.5	20.0	23.5
immune-stimulation + surgery	0	–	0.5	–	3.0	4.5	6.0	8.5	11.0	14.5	18.0	21.5	
				2.0	3.5	5.0	6.5	9.0	11.5	15.0	18.5	22.0	



Let $z^j(t) \in R^m$, $j = 1,\ldots,M$, $t \in \Theta$ be a vector of measured clinical data from the j-th patient. If $z(t)$ is measuring continuously then we can consider the integral of $z(t)$ on $[0,t]$

$$I_z(t) = \int_0^t z(u)\,du \ . \tag{4.1}$$

The average value of $z(t)$ on $[0,t]$ is

$$\bar{z}_t = \frac{1}{t} I_z(t) \ . \tag{4.2}$$

We have measurements of $z(t)$ only at the discrete set of instants of time $\Theta = \{t_1,\ldots,t_N\}$. Then instead of $I_z(t)$ we estimate by

$$\hat{I}_z(t) = \sum_{t_i<t} \frac{1}{2}(t_i - t_{i-1})(z_{t_i} - z_{t_{i-1}}) \ , \tag{4.3}$$

$$t_0 = 0, \ \ t_i \in \Theta \ .$$

Consequently a set of values of immunological data $z = \{z_t,\ t \in \Theta\}$ can be approximated as a set of values $\hat{X} = \{\hat{x}_t = \frac{1}{t}\hat{I}_z(t),\ t \in \Theta\}$

$$\begin{array}{c} z^j_{t_1}, \ldots, z^j_{t_N} \\ \downarrow \qquad\quad \downarrow \\ \hat{x}^j_{t_1}, \ldots, \hat{x}^j_{t_N} \end{array} \quad j = 1,\ldots,M \ . \tag{4.4}$$

The variables $\hat{x}(t)$ describe the average dynamics of $z(t)$ in time.

4.2. Basis dynamics of immunological data

To study the characteristics of the immune system many tests are performed, but not all of these tests are informative for the tumor process. For example, we can use immunological tests of the first level which are measured in the blood of patients such as:

— concentration of B-cells $= x_1$ — T-cells % / B-cells % $= x_2$ — concentration of immunoglobylius (Ig) of a different class (M,G,A) — $IgG = x_3$ — $IgA/IgM = x_4$ — Lymphocytes % $= x_5$

To construct the basis dynamics of immunological data we use a group of patients with life span after operation of not less than 60 months. Some examples of individual trajectories for these tests are presented in Fig. 3.

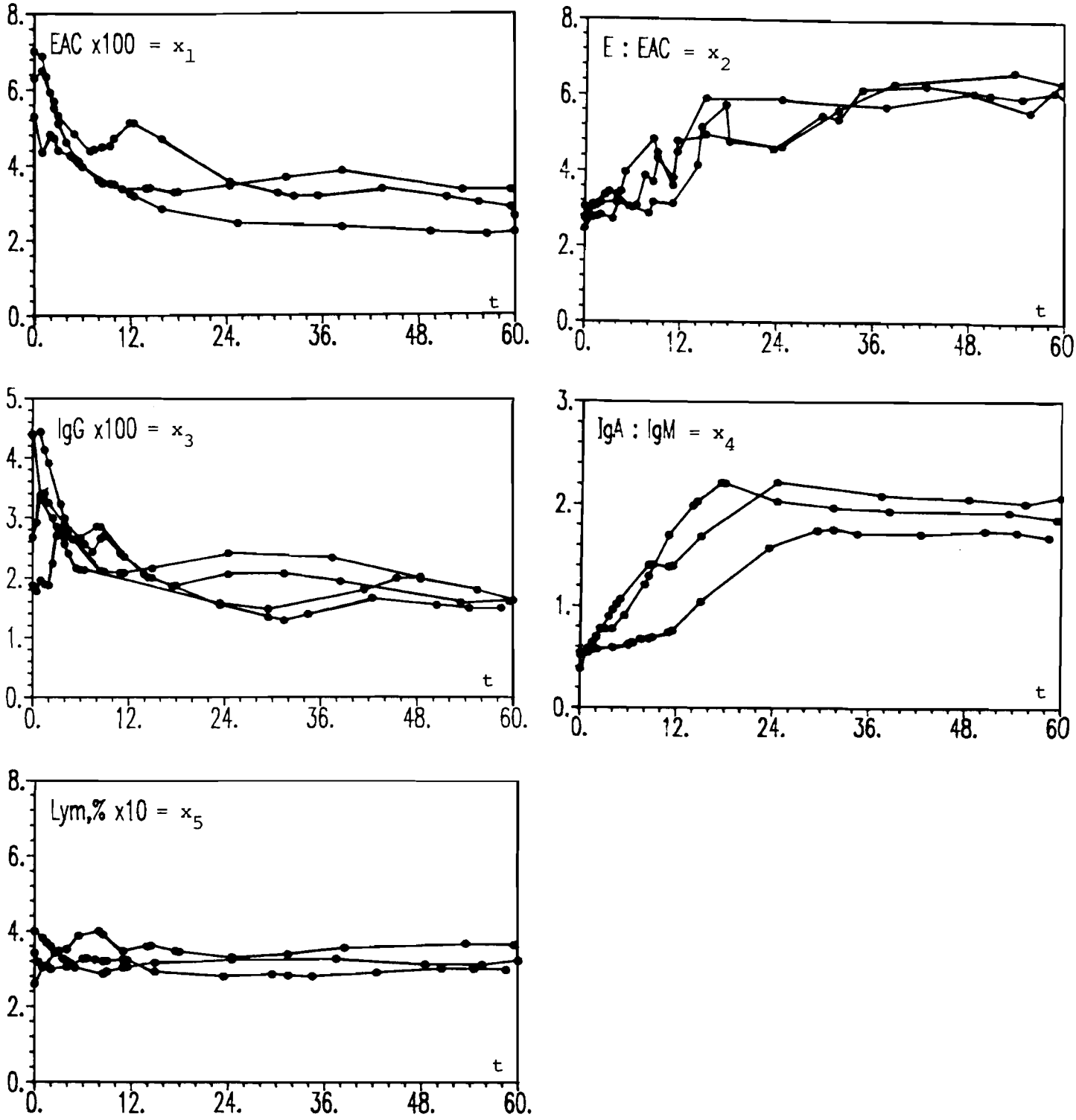


Fig. 3. Examples of individual trajectories of the immunological data dynamics from the group of patients with the best clinical form of disease. x_1 is concentration of B-cells; x_2 is $\frac{\text{T-cells\%}}{\text{B-cells\%}}$, x_3 is IgG, $X_4$is IgA/IgG, x_5 is Lymf. %, t is time in months.

B-cells

The average dynamics of B-cells after surgery in the group of patients with the best clinical form of disease is approximated by equation

$$\frac{d}{dt}x_1(t) = \alpha_{10} - \alpha_{11}x_1(t)\ ,\ \ x_1(0) = x_{10}\ . \tag{4.5}$$

In this case $x_1(t)$ decreased from the initial value x_{10} to the stationary level $x_1^* = \alpha_{10}/\alpha_{11}$. On Fig. 4 the solution of the equation (4.5) (continuous curve) and experimental data ($\bullet$) are described. Parameters of equation (4.5) and the initial value was estimated by means of the methods which are discussed in Section 3.

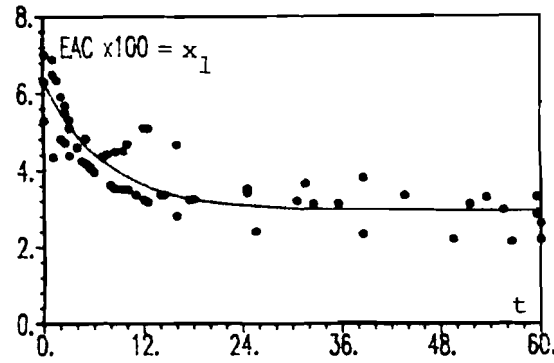


Fig. 4. Average dynamics of B-cells $= x_1$ in the group of patients with the best clinical form of disease. The continuous curve is the solution of equation (4.5) and the points ($\cdot$) are experimental data ($\alpha_{10} = 0.39$, $\alpha_{11} = 0.13$, $x_{10} = 6.29$).

T-cells % / B-cells %

In this case we use equation

$$\frac{d}{dt}x_2(t) = \alpha_{20} + \alpha_{21}x_2(t) - \alpha_{22}x_2(t)x_2(t)\ , \tag{4.6}$$

$$x_2(0) = x_{20}$$

Fig. 5 describes the average dynamic behavior of this variable $x_2(t)$.

Immunoglobulin IgG

The equation for the average dynamics has the form

$$\frac{d}{dt}x_3(t) = \alpha_{30} - \alpha_{31}x_3(t)\ ,\ \ x_3(0) = x_{30}\ . \tag{4.7}$$

See Fig. 6.

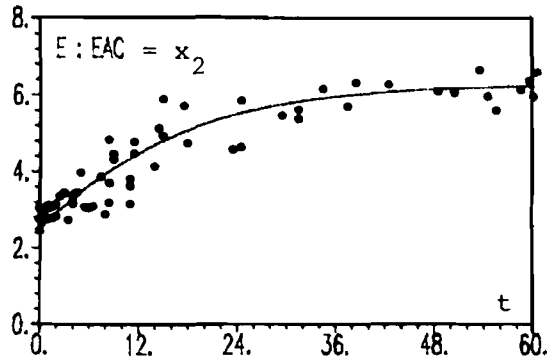


Fig. 5. Average dynamics of T-cells%/B-cells% in the group of patients with the best clinical form of disease. ($\alpha_{20} = 0.24$, $\alpha_{21} = 0.000001$, $\alpha_{22} = 0.006$, $x_{20} = 2.5$).

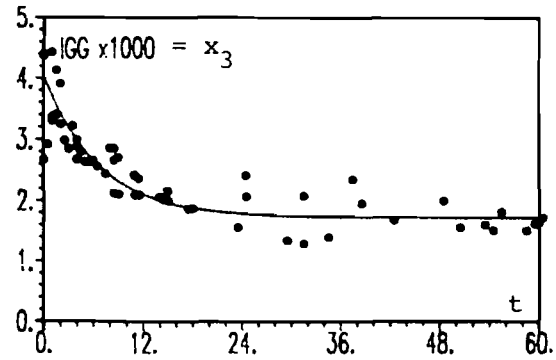


Fig. 6. Average dynamics of IgG in the group of patients with the best clinical form of disease. ($\alpha_{30} = 0.25$, $\alpha_{31} = 0.15$, $x_{30} = 4.13$).

Immunoglubulius IgA / IgM

The equation has the form

$$\frac{d}{dt}x_4(t) = \alpha_{40} + \alpha_{41}x_4(t) - \alpha_{42}x_4(t)x_4(t)\ ,\ \ x_4(0) = x_{40}\ . \tag{4.8}$$

The average dynamics for this variable $x_4(t)$ is represented in Fig. 7.

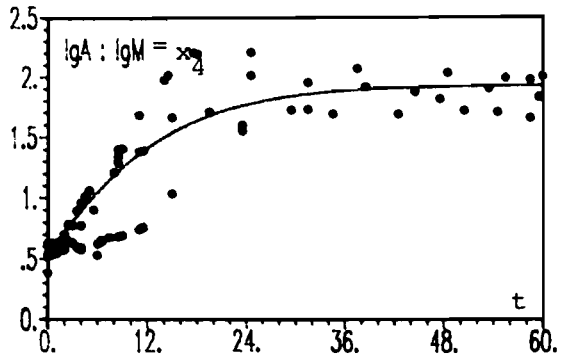


Fig. 7. Average dynamics of IgA/IgM in the group of patients with the best clinical form of disease. ($\alpha_{40} = 0.1$, $\alpha_{41} = 0.00001$, $\alpha_{42} = 0.02$, $x_{40} = 4.13$).

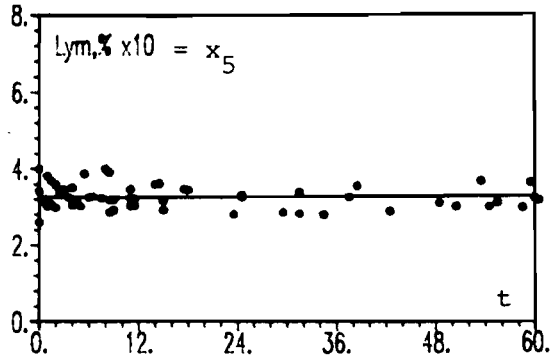


Fig. 8. Average dynamics of Lymphocyte% in the group of patients with the best clinical form of disease. ($x_{50} = 0.38$)

4.3. Character of deviations from average dynamics

Stable deviation of immunological values from average dynamics is an important characteristic of the tumor process. Consider the dynamics of deviations from the basis solution in the different groups of patients with respect to life span.

We expect that small deviations will be characteristic for the patients with the best clinical form of disease. For the patients with a short life span after surgery, this deviations will be greater than in the first group. In Table 1 (Section 2.2) the average square of deviations for the different groups is represented. Consequently, we have a correlation between the values of deviations from the basis trajectories and life span, moreover the value of deviations are significant. Therefore we can study the square of deviations or data variance.

4.4. Immunological data and mortality dynamics

Using methods from Section 3 and assuming that the matrices Q and Γ are diagonal we have an estimation for $\hat{Q}$ and $\hat{\Gamma}$. In our case these estimates have values

$$\hat{Q} = \begin{bmatrix} 0.0001 & & & \\ & 0.0074 & & \\ & & 0.0102 & \\ & & & 0.0038 \end{bmatrix}$$

$$\hat{\Gamma} = \begin{bmatrix} 0.0324 & & & \\ & 0.0001 & & \\ & & 0.10 & \\ & & & 0.015 \end{bmatrix}$$

In Fig. 9 the estimation of the survivor function is represented and in Fig. 10 the solutions for $m_i(t)$, $\gamma_i(t)$, $i = 1,\ldots,4$ from the system (2.16) with the estimation $\hat{Q}$, $\hat{\Gamma}$ are represented.

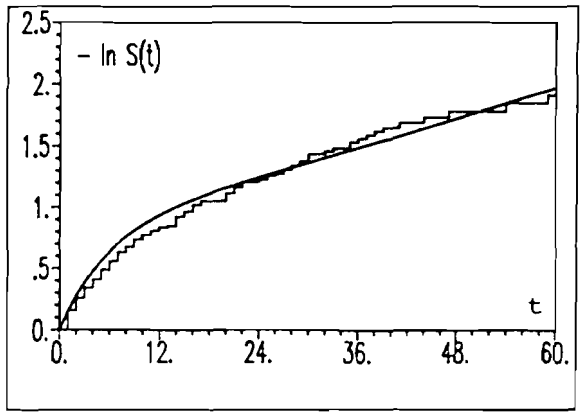


Fig. 9. The estimation of the survivor function from (2.16)

Now, for the individual estimation of the disease activity during treatment we can use an index

$$\hat{\mu}_t = \sum_{i=1}^{4} \hat{Q}_{ii}\, \hat{x}_i^2 , \quad t \in \Theta \tag{4.10}$$

or

$$\hat{M}_t = \int_0^t \sum_{i=1}^{4} \hat{Q}_{ii}\, \hat{x}_i^2 . \tag{4.11}$$

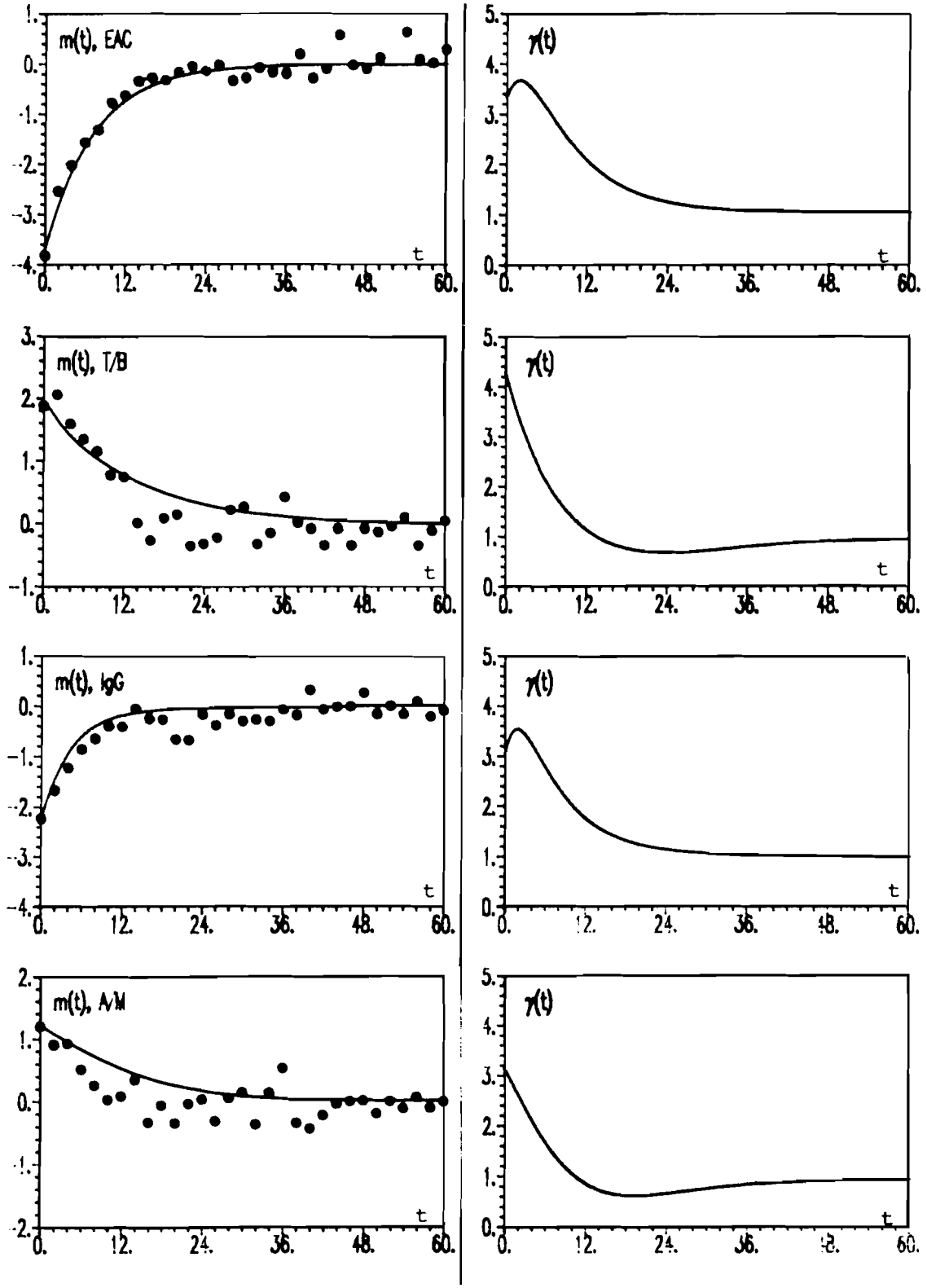


Fig. 10. Results of estimating of the parameters of the model (2.16) by basis equation and survivor function. Lymphocyte% is not used.

This index can consider the intensity of the pahological process for this level of immunological data deviations.

In Fig. 11 individual estimations $\hat{M}_t^i$ for two different, by life span after surgery, groups are represented.

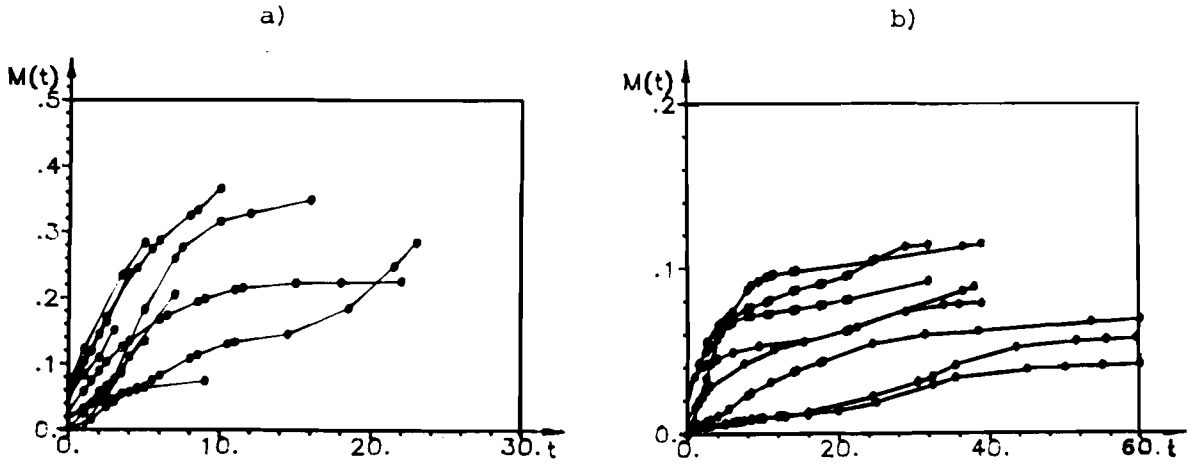


Fig. 11. Individual estimations $\hat{M}$ for two groups of patients: a) $T \geq 40$ months, b) $T < 40$ months.

We can see that the dynamics of the estimation $\hat{M}_t$ differ in the groups of patients with different life spans after the beginning of treatment. The using these estimated indices we can attempt to control the individual dynamics of the disease during the treatment.

5. Discussion

The method of analysis of disease dynamics for oncological patients is represented in this work; the basis on the study of mortality dynamics as a function of immunological data deviations allows us to estimate the clinically unexpressed remainder of the tumor process and to inspect this process during treatment in individual patients by measuring in clincial immunological indices. With the help of such estimations we can solve various practical problems such as estimating the state of the organism, investigating the process dynamics, comparing the effectiveness of different treatments and formulating the optimal control problem for process treatment. But these problems are beyond the frame of this presentation.

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