SECTION 1
THE PROCEDURE FOR CONSTRUCTING MATHEMATICAL MODELS OF PATHOLOGICAL PROCESSES BASED ON THE EQUATIONS OF POPULATION DYNAMICS

When conducting systematic medical research, questions arise about predicting not only the quantitative, but also the qualitative behavior of the disease. This is, first of all, a form of the pathological process, which is influenced by a number of uncertainties - the time of formation of a cascade of specific plasma cells, the effect of the damaged organ on the immune response, the treatment regimen, etc. Solving problems of this kind requires the development of appropriate algorithms for system analysis.

This section defines the main stages of the complex analysis of medical scientific research – construction of mathematical models of pathological processes, their decomposition and aggregation, identification of parameters, development of methods of qualitative analysis – conditions for the stability of trajectories in the classification of forms of pathological processes, formulation and solution of problems of optimal control in the provision of treatment, the issue of bifurcations and chaos when changing the parameters of models of pathological processes, as well as development of an appropriate software environment to support systemic medical research.

In addition, the section begins the implementation of the stages of system analysis. Namely, the construction of mathematical models of pathological processes in the class of equations of population dynamics will be carried out.

1.1. System analysis of medical scientific research in the dynamics of pathological processes

In this subsection, we will talk about the heuristic stage of system analysis in solving problems of medical science. System analysis arose in response to the requirements of practice, which put us in front of the need to study and design complex systems, manage them in conditions of incompleteness of information, limited resources, and lack of time. To this day, there are ongoing discussions about whether systems analysis can be considered a science, an art or a "technological craft". The application of system analysis to problems related to "sociotechnical", "social" systems, i.e. systems in which people play a decisive role, is especially hotly debated [77]. When solving such problems, not only the issues of building and using models, not only heuristic searches for solutions to poorly structured, not fully formalized problems, but also purely psychological aspects of human relationships are essential, which further "separates" system analysis from "pure sciences", such as physics and mathematics [36].

In the paper [62], a reference scheme of the algorithm for setting problems of applied system research of a real problem is proposed and substantiated. Let's apply it to solving the problem of developing an algorithm for studying the dynamics of human disease (Appendix G.1).

Algorithm of applied system analysis.

Initial statement of the problem. A disease means a violation of the normal functioning of the body caused by functional and (or) morphological changes [1, 61]. The occurrence of diseases is associated with the impact on the body of harmful factors of the external environment (physical, chemical, biological, social), as well as with its genetic defects, etc.

The study of the causes of diseases and the mechanisms of their development (in order to control them), as well as the study of the nature of the body's reverse reactions to therapeutic effects, is the main task of medical science.

Treatment of the disease is carried out by three main methods: drug (or pharmacological), surgical (or surgical), natural (or biophysical).

Such a multiplicity of treatment methods, as well as incompleteness of information on the causes and mechanisms of the course of the disease, constitute a problem that must be solved by the algorithm of system analysis.

Particular difficulties are associated with the definition of the concept of "disease", since this concept should include only such signs of the disease that are characteristic of its arbitrary forms. At the same time, the clinical picture of various diseases and their significance for a person and society are very variable [61].

In addition, it should be noted that biological systems (which should be taken into account when studying the disease) are complex control systems, in which it is often difficult to separate the control object from the regulator itself.

Setting models. A meaningful model of the pathological process at the cellular level is presented in the works [1,53,61]. Having carried out its decomposition, at the first level we get fragments:

- the cause of the disease;
- the state of reactivity of the immune system;
- features of the structural and functional organization of body systems.

The fragment "cause of the disease" is non-elementary, but in our model it is recognized by experts as finite, since it does not lend itself to further decomposition. In different models [23,53], the cause of the disease is determined both by the presence of own modified cells (cancer cells) in foreign bodies (viruses, bacteria) and by the absence of certain cellular structures (loss of the T-helper subpopulation in AIDS). Mathematical models for describing disease factors – logistic type or Gompertz dynamics [118].

The fragment "state of reactivity of the immune system" is non-elementary (a generalized model of immunity is presented in [53]). As a result of its simplified decomposition, as it is done in [53], we come to elementary fragments:

-Antibodies;

- plasma cells.

To describe the immune system, the model of G.I. Marchuk is used, represented by a system of nonlinear differential equations with a delay.

Features of the structural and functional organization of body systems significantly affect the dynamics of the disease. It should also be taken into account during treatment. As a result of decomposition at the first level, we get:

- the degree of damage to the organ (system, body);
- toxicity of treatment.

The fragment "degree of organ damage" is final. It is determined by a percentage that depends on the volume of the "causative agent" of the disease.

The toxicity of treatment is determined by a number of indicators of the functioning of organs and systems. At the cellular level, this can be: NK activity, macrophage activity, bone tissue condition, etc. To define models, the use of integro-differential models with memory will be proposed here.

Identification of model parameters. As mentioned above, models of population dynamics are used for different fragments of the disease system, which are quite often non-linear, and the parameters to be identified are elements of the Hilbert space.

Definition of the configurator. To describe the experimental system of the pathological process, the language of dynamic systems was used.

The models used belong to the class of equations of population dynamics. At different stages of system analysis, it will be necessary to apply the apparatus of the qualitative theory of dynamical systems.

The language of medical science should also be included in the configurator -- at least for the formulation of biological consequences (as it is done in [53]), which should be available to doctors. For clinicians, the results of the system analysis should be submitted in the form of regulations approved by the Ministry of Health (information sheets, recommendations, etc.).

Subsection 7.2 will present one of the software standards, in which it is possible to publish the results of a systematic analysis of the pathological process.

Identification of the parties involved. The results of the systematic analysis of the disease may concern specialists in medical and biological cybernetics, theoretical doctors, and clinical medicine specialists.

Definition of interests.

Specialists in medical and biological cybernetics are interested in the implementation of the methods of the theory of automata, the theory of algorithms, the general theory of systems, the theory of complex control systems and the theory of automatic regulation and control in the study of the causes and mechanisms of the disease.

Theoretical physicians would like to study the vital activity of both the whole organism and its individual parts - cells, organs, functional systems in the conditions of the disease.

Clinicians strive to obtain effective ways to treat the disease along with their justification.

Definition of problems. The most crucial stage of system analysis, which is its entry point, is the formulation of problems. At the same time, it is necessary to identify all those who will be affected by possible changes based on the results of system analysis, and formulate their problems arising from these changes in all languages of the configurator [62]. The resulting set of problems is the problem.

Thus, specialists in the field of medical and biological cybernetics will be concerned with the problems arising from the emergence of new mathematical models and problems of their qualitative analysis – this requires further development of the mathematical apparatus of infinite-dimensional systems of population dynamics. The technical implementation of the results obtained requires the development of software with new accessible interfaces for users who are not specialists in the field of dynamic systems.

For theoretical physicians, problems arise related to the substantiation of the biological consequences obtained from the point of view of medical science (physiology, pathology, etc.).

For clinicians, these are the problems of formulating the obtained numerical algorithms in terms of treatment methods, as well as the problems of modifying algorithms taking into account multiple pathologies, complications during treatment, etc.

Identifying goals. Taking into account the comments expressed in [62] regarding the setting of goals (multiplicity, correct ranking, change over time, etc.), we come to the following set of goals in the study of the dynamics of the development of the pathological process:

1. Study the cause of the disease (the behavior of foreign bodies or their own genetically deformed cells).
2. To study the mechanisms of development and course of the disease.
3. Study the body's reverse reaction to damage.
4. Determine the body's backlash after treatment.
5. Suggest optimal treatment regimens.

Generation of alternatives

At this stage, we will form the following alternatives – ways to solve the problem (i.e. achieve goals).

1. Pathological anatomy and histology, the tasks of which are:

- to study morphological changes in organs, tissues and cells in diseases, as well as recovery processes;

- to find out the causes, mechanisms and dynamics of these changes;

- to compare morphological changes with the results of clinical, biochemical and pathophysiological studies.

At the same time, the object of research is the material obtained during the concealment of those who died from diseases, organs and tissues removed during surgical interventions and excised for diagnostic purposes, as well as material

taken from laboratory animals that were exposed to various influences under experimental conditions [1].

2. Pathological physiology, the tasks of which are:

- to study the general patterns of a functional nature at the level of the cell, organs, systems and the body as a whole, which determine the occurrence and course of the disease,

- to study the mechanisms of resistance, pre-disease, recovery and the consequences of the disease.

The main method of studying pathological physiology is an experiment on animals. Animal experiments are significantly supplemented by studies of pathophysiological patterns in the clinic (clinical pathophysiology) using harmless methods of studying the functions of organs and systems (teleelectrophysiological, X-ray, radiographic, biochemical, immunological, etc.), various functional tests [61].

3. Clinical biochemistry (laboratory and clinical diagnostics)

- to study biochemical processes (at the level of molecular reactions) in the human body in pathological conditions and under therapeutic effects;

- to develop methods for detecting these changes in order to diagnose and prognosis diseases

- to develop rational methods of active influence with the help of various chemical compounds on the course of biochemical reactions in the body for the treatment or prevention of certain pathological conditions.

The object of research is experimental pathological conditions simulated on various laboratory animals (but not on humans), which are investigated by methods already tested in the field of molecular biology and general biochemistry [27]

study the disorders of molecular reactions

4. Medical Microbiology and Virology

- to study microorganisms pathogenic for humans;

- to study the mechanisms of pathogenic action of pathogenic microorganisms;

- to study the body's protective reactions that occur in response to the action of microorganisms that can cause disease.

Medical microbiology uses biological methods (isolation of pure cultures), methods of genetics of microorganisms, microscopy, biochemistry, molecular biology, biophysics depending on the tasks and goals of the study [76]

5. Experimental medicine (experimental nosology), the tasks of which are:

- to reproduce individual symptoms or syndromes of human disease in animals in order to find out the basic patterns of the pathogenesis of human disease;

- to reproduce various pathological processes and conditions in animals in order to test new drugs and study the mechanisms of recovery.

The objects of research are laboratory animals exposed to pathological effects.

6. Physical modeling

- to study pathological processes based on models that are their physical analogues.

7. Mathematical modeling [170]

- to study diseases on the basis of mathematical models, which are their formalized descriptions.

In this case, great weight should be given to the pathological process as a sequence of reactions naturally occurring in the body to the damaging effect of a pathogenic factor. In fact, each disease consists of a certain set of pathological processes (however, the disease is not just the sum of pathological processes) [61].

Definition of criteria. Based on the provision [62] on "criterion as a quantitative model of qualitative goals", the following list is proposed:

a) general requirements related to the quality of performance of its functions by the optimal system and its implementation:

- functionality, i.e. the suitability of the alternative to achieve the goal. In the context of this work, an alternative is functional if it provides an adequate identification of the pathological process and reflects the dynamics of its development;
- classification error. It is assumed that there is an independent expert who determines the discrepancy between the accepted alternative and a reliable answer;
- the multiplicity of pathological processes to which the alternative of study can be extended;
- logical complexity. Often, more reliable alternatives are also more complex;

b) specific requirements arising from their use for the synthesis and adaptation of optimal treatment regimens:

- the ability to develop treatment regimens to put the disease into remission;
- the ability to develop treatment regimens with maximum prolongation of life, while guaranteeing its quality;
- the ability to develop treatment regimens with minimal toxicity, while maintaining cell cycles;
- the ability to develop treatment regimens while maintaining the biological age of a person.

Aggregation of criteria. It is proposed to introduce the concept of an integral quality criterion of the method of studying the disease. For a qualitative assessment of the integral criterion, it is possible to propose a method of reducing a multi-criteria problem to a single-criterion one [62].

Building an ideal system

Based on the choice of many alternatives, taking into account the integral criterion of quality, we come to the following sequence of questions regarding the study of the causes and mechanisms of the development of the pathological process.

1. Conditions of existence and uniformity of solutions in equations of the generalized model of Gompertz dynamics, integro-differential models with memory.
2. Identification of parameters in models of pathological processes.
3. Conditions for classifying the forms of the course of the disease on the basis of the apparatus of the theory of stability.
4. Setting and solving control problems with phase constraints to establish optimal treatment methods. Problems of decision-making under conditions of uncertainty.
5. Bifurcations and periodic solutions in disease models. Conditions for the occurrence of a chronic form of the disease.

1.2. Mathematical models of population dynamics

In the work [99] a fundamental description of biological concepts such as predator-prey, competition and cooperation (or mutualism) was introduced. Thus, most models of population dynamics based on differential equations come from the following equation:

$$\frac{dN(t)}{dt} = \left\{ \begin{array}{l} \text{внесок індивідуума} \\ \text{у зміну популяції за} \\ \text{одиницю часу} \end{array} \right\} N(t) \qquad (1.2.1)$$

Here $N(t)$ is the population density (or biomass) of one species at a time t. Regarding the multiplier inside the parentheses in (1.2.1), assumptions are made based on the behavior of the system under study.

In particular, if it is assumed that the individual contribution to the change in the population per unit of time is a function $F(t,N)$ defined for all $t > t_0,\ N \geq 0$ then the so-called Kolmogorov model is obtained on the basis of (1.2.1):

$$\frac{dN(t)}{dt} = F(t, N(t))N(t). \tag{1.2.2}$$

The choice of the function F , together with biological assumptions such as the invariance in time of the medium and the dependence of the density, lead to the known ordinary differential equations of population dynamics. For example, if $F(t,N) \equiv \alpha$ (positive constant), we get the Malthus model:

$$\frac{dN(t)}{dt} = \alpha N(t).$$

If we assume that $F(t,N) \equiv \alpha - (\alpha / k)N$ for some positive constants α and k, then we get the well-known logistic equation:

$$\frac{dN(t)}{dt} = \alpha N(t)\left\{1 - \frac{N(t)}{K}\right\}. \tag{1.2.3}$$

The paper [131] presents a constructive method of constructing a logistic equation for the size of a species population. To do this, enter the following six parameters:

- $f \in (0,1)$ - instant fertility;
- $r \in (0,1)$ - instant mortality;

- $c \in (0,1)$ - the coefficient of proportionality to the number of N persons meeting during a short period of time. That is, cN this is the number of contacts within a short period of time;

- P - the likelihood that no meeting will lead to offspring;

- k - tolerable volume of the environment in terms of the maximum number of individuals that the environment can support;

- N_0 - the initial abundance of the species within a given area (site); t_0 - the initial point in time at which this number exists.

The model looks like:

$$\frac{dN}{dt} = f\left(1 - P^{cN}\right)N - rN - \left(f - r\right)\frac{N^2}{k}. \qquad (1.2.4)$$

Since equation (1.2.3) implies a monotonic direction at $t \to \infty$ population density to the equilibrium state $N(t) \equiv k$, it would be desirable to find modifications (1.2.3) to obtain non-monotonic (with fluctuations) solutions of the model equations. If they put

$$F(t,N) \equiv \alpha - \left(\frac{\alpha}{k}\right)N(t-\tau)$$

for some constant $\tau > 0$, then (1.2.2) leads to Hutchinson's logistic equation [62]:

$$\frac{dN(t)}{dt} = \alpha N(t)\left\{1 - \frac{N(t-\tau)}{k}\right\} \qquad (1.2.5)$$

Instead of a single discrete delay, as in (1.2.5) you can put

$$F(t,N)=\alpha-\frac{\alpha}{K}N(t)-\int_{-\infty}^{t}H(t-s)G(N(s))ds \qquad (1.2.6)$$

where H is the integral scalar function, and is G the integral function of ; N if (1.2.6) is used in (1.2.2), then we get Voltaire's model of a population that pollutes its own environment and pollution has an accumulating toxic effect. Thus, the equation is obtained in the form:

$$\frac{dN(t)}{dt}=N(t)\left\{\alpha-(\alpha/k)N(t)-\int_{-\infty}^{t}H(t-s)G\big(N(s)\big)ds\right\}$$

studied by many authors under different conditions on H and G [99].

One of the significant advantages in obtaining different models based on (1.2.2) is the non-negativity of solutions under non-negative initial conditions. This follows from the following representation $N(t)$ at $t>0$:

$$N(t)=N(0)\exp\left[\int_{0}^{t}F(s,N(s))ds\right]$$

The starting point in obtaining models based on the equations with a delay in birth and mortality is the balance equation (provided that there are no immigrations and emigrations):

$$\frac{dN(t)}{dt}=\text{народжуваність - смертність} \qquad (1.2.7)$$

For example, if we consider a population of adult cells, then the fertility of cells at time t depends on the population of adult cells at time $t-\tau$, where τ is

the time it takes for a newly formed cell to become an adult. If fertility and mortality are governed by density-dependent factors, then with (1.2.7) we get:

$$\frac{dN(t)}{dt} = b(N(t-\tau)) - m(N(t)) \qquad (1.2.8)$$

where functions $b(\bullet)$ and $m(\bullet)$ denote density-dependent fertility and mortality, respectively. If the time delays in (1.2.8) are continuously distributed, then instead of (1.2.8) we can consider an equation of the form:

$$\frac{dN(t)}{dt} = b\left(\int_{-\infty}^{t} H(t-s)N(s)ds\right) - m\big(N(t)\big),$$

or what's the same

$$\frac{dN(t)}{dt} = b\left(\int_{0}^{\infty} H(s)N(t-s)ds\right) - m\big(N(t)\big) \qquad (1.2.9)$$

where the lagging H nucleus means the distribution of the density of the past or the effects of the aftereffect on the current fertility.

Unfortunately, compared to equations of type (1.2.2), it is not obvious that the required non-negative initial conditions in (1.2.8) and (1.2.9) will result in the non-negativity of solutions (1.2.8) and (1.2.9).

The paper [99] shows that in the class of population systems, delays in birth and mortality do not destabilize the system if the self-regulating inverse relationship is strong enough compared to the effects of interaction and if the self-regulating inverse relationship is realized without any time delays or with sufficiently small delays.

According to the results of the work [90], due to random factors, such as various stresses for the human body, and in the wild, for example, droughts, fertility and mortality are modeled by functions from stochastic processes, which in turn are determined by solutions of their own stochastic differential equations, the consideration of which is beyond the scope of this study.

1.3. Integro-differential models with memory

In the study of a number of dynamic processes in biology and medicine [99,106,107,120], models based on integrodifferential equations with a delay are encountered:

$$\frac{dx_i(t)}{dt} = x_i(t)(b_i + \sum_{j=1}^{n} a_{ij}x_j(t) + \sum_{j=1}^{n} b_{ij}x_j(t-\tau_{ij}) + \\ + \sum_{j=1}^{n} c_{ij}\int_{-\infty}^{t} k_{ij}(t-s)x_j(s)ds), t>0, i=1,2...n \quad (1.3.1)$$

Equations (1.3.1) describe populations that pollute their own environment [99]. At the same time, pollution has an accumulating toxic effect, which is described in equations (1.3.1) by members of the

$$\int_{-\infty}^{t} k_{ij}(t-s)x_j(s)ds$$

Let us point out some physical and technical applications of integro-differential equations: a model of labor productivity due to fatigue, a problem on the theory of electrical circuits in the presence of the phenomenon of hysteresis [22, p.134-135], the Boltzmann kinetic equation of an ideal monatomic gas taking into account the collision of particles [81], a description of the propagation of nonlinear waves in dispersing and dissipative media (Wisem's equation),

hydrodynamics of non-isothermal plasma without collisions and the study of the so-called stratified (stratific) environments [78].

Integro-differential equations with a delay are also used to describe populations that "do not know" the exact value of the maturation period of individuals [106]:

$$\frac{dx_i(t)}{dt} = b_i x_i(t) + \sum_{j=1}^{n} c_{ij} \int_{-\infty}^{t-\tau_m} k_{ij}(t-s) x_j(s) ds \qquad (1.3.2)$$

Here $b_i < 0$ is the rate of accidental disappearance of individuals, τ_m - the minimum period of delay in the maturation of individuals, $k_{ij}(\tau)$ - the density of distribution of the maturation period.

With different expressions for a function $k_{ij}(\tau)$, the properties of solutions were studied in papers [99,106].

So, if $k_{ij}(\tau)$ is the density of distribution, then by definition it must satisfy the condition of rationing:

$$\int_0^{\infty} k_{ij}(s) ds = 1 \qquad (1.3.3)$$

In the paper [106], when modeling the population of circulating white blood cells using (1.3.2), $k_{ij}(\tau)$ the gamma distribution density was chosen as the following:

$$k_{ij}^{\Gamma}(\tau) = \begin{cases} 0, \tau \le \tau_{m,} \\ \dfrac{a^{m+1}}{\Gamma(m+1)} (\tau - \tau_m)^m e^{-a(\tau-\tau_m)}, \tau > \tau_{m,} \end{cases} \qquad (1.3.4)$$

where $a, m \geq 0$

As shown in [106,107], this choice $k_{ij}(\tau)$ is in good agreement with the experimental data and is a confirmation of previous results on the correspondence of cell cycles to gamma distribution.

In addition, as shown in papers [123,117] at natural values of *m* by introducing auxiliary variables

$$x_{n+j}(t) = \int_{-\infty}^{t} k_{ij}^{T}(t-s)x_j(s)ds, t > 0, j = \overline{1,n} \tag{1.3.5}$$

Systems of integro-differential equations (1.3.1), (1.3.2) can be reduced to ordinary differential equations or to differential equations with discrete delays.

In the paper [99] for the system (1.3.1), the conditions for the existence of the solution and the global attractor in the absence of instantaneous responses in population change and discrete delays are formulated, i.e. when:

$$a_{ij} = 0, \quad b_{ij} = 0, \quad i, j = \overline{1,n}$$

The conditions are reduced to the positive certainty of the integral nucleus, introduced using the following concept [99].

Definition 1.3.1. Let K – $n \times n$ – a matrix with elements $(K)_{ij} = -c_{ij}k_{ij}$, where $c_{ij}, i.j = \overline{1,n}$ are the real constants, $k_{ij} : [0,\infty) \to (-\infty,\infty)$ are such that:

$$\int_0^{\infty} k_{ij}(s)ds = 1, \quad \int_0^{\infty} \left|k_{ij}(s)\right|ds < \infty, \quad \int_0^{T} (k_{ij}(s))^2 ds < \infty, i = \overline{1,n} \tag{1.3.6}$$

for arbitrary $T > 0$. A matrix kernel K is called positively defined if for an arbitrary vector function

$f=(f_1, f_2,..., f_n), f_j:[0,\infty)\to(-\infty,\infty), f_j\in C[0,T], T>0$ there is a positive constant μ such that

$$\sum_{i=1}^{n}\int_0^T f_i(t)\left(\int_0^t \sum_{j=1}^{n} -c_{ij}k_{ij}(s)\,f_j(t-s)ds\right)dt \geq \mu\int_0^T\left\{\sum_{i=1}^{n} f_i^{\,2}(t)\right\}dt, \tag{1.3.7}$$

for an arbitrary finite $T>0$.

When modeling a number of social and economic systems, models with managed memory were used [86]. Guided memory patterns occur naturally in populations of blood cells or bone tissue cells. The body itself regulates the time it takes for cells to mature or reach senescence. At the same time, both external (physical exertion, extreme situations, man-made factors) and internal (the state of physiological systems, biological age of a person, protective functions of the body) factors are taken into account.

The use of integro-differential models with memory requires the development of a mathematical apparatus for the problems of the existence of solutions, stability, as well as the evaluation of model parameters. The following sections will be devoted to these issues.

Mathematical statement of the problem. In this subsection, the results of the work [99,106,107,120] on the study of systems (1.3.1), (1.3.2) will be transferred to integro-differential equations with a delay with memory:

$$\frac{dx_i(t)}{dt} = x_i(t)\left(b_i + \sum_{j=1}^{n} c_{ij}\int_{z(t)}^{t} k_{ij}(t-s)x_j(s)ds\right), t>0, i=\overline{1,n} \tag{1.3.8}$$

Here $z(t) < t$ is the time limit for the aging of individuals. It is assumed that $z(t) \in C[0,\infty)$, . $x_i(t) \in C^1[0,\infty)$

That is, individuals born before the moment $z(t)$ in the moment t do not take part in reproduction.

Let (1.3.8) be given the following continuous initial conditions on $[z_*, 0]$, where $z_{/} = \inf_{t \geq 0} z(t)$:

$$x_i(s) = \varphi_i(s) \geq 0; \quad \varphi_i : [z_*, 0] \to [0,\infty); \varphi_i(0) > 0; \tag{1.3.9}$$

$$\sup_{s \in [z_*, 0]} \varphi_i(s) < \infty$$

We assume that equations (1.3.8) are such that the linear system:

$$\sum_{j=1}^{n} c_{ij} \int_0^{t-z(t)} k_{ij}(s) ds x_j^* = -b_i, i = \overline{1,n} \tag{1.3.10}$$

has a positive solution:

$$x^* = (x_1^*, x_2^*, ..., x_n^*), x_i^* > 0, i = \overline{1,n}.$$

The objectives of this work are: to present the conditions for the existence of the global attractor of the problem (1.3.8), (1.3.9); to show a method for estimating the parameters of this model (including the integral core) based on experimental data.

Conditions for the existence of a global attractor. Next, we will show the conditions under which x^* - the global attractor of the system (1.3.8), (1.3.9).

Lemma 1.3.1. Suppose that the solution (1.3.8), (1.3.9) exists on some interval $[0,t]$. Then it is non-negative:

$$x_i(t) \geq 0, i = \overline{1,n}$$

The proof is given in Appendix A.1.

Definition 1.3.2. Let K be – $n \times n$ is the matrix for which the conditions are met (1.3.6). A matrix kernel K is called **positively defined with respect to the memory function** $z(t)$ **if** for an arbitrary vector function

$$f = (f_1, f_2, ..., f_n),\ f_j : [0,\infty) \to (-\infty,\infty),\ f_j \in C[0,T], T > 0$$

There is a positive constant μ such that

$$\sum_{i=1}^{n} \int_0^{T-z(T)\eta(z(T))} f_i(t)\Big(\int_0^{t-z(t)\eta(z(t))} \sum_{j=1}^{n} -c_{ij}k_{ij}(s) f_j(t-s)ds\Big)dt \geq \mu \int_0^{T-z(T)\eta(z(T))} \Big\{ \sum_{i=1}^{n} f_i^2(t) \Big\} dt,$$

for an arbitrary finite $T > 0$. Here $\eta(t) = \begin{cases} 1, t \geq 0 \\ 0, t < 0 \end{cases}$ is a unit function.

Theorem 1.3.1. Let the system (1.3.8) satisfy the following requirements:

1) condition (1.3.10) is met;
2) The integral core of the system (1.3.8) is positively defined with respect to the memory function $z(t)$.

Then the solution of the system (1.3.8) exists at arbitrary $t \geq 0$.

The proof is given in Appendix A.1**.**

When proving the existence of a global attractor, we will use the result of the work [116].

Lemma 1.3.2. Let $f(t)$ be an integral function defined on $[0,\infty)$ and such that $f(t)$ is integrated on $[0,\infty)$ and uniformly continuous on $[0,\infty)$. Then:

$$\lim_{t\to\infty} f(t) = 0.$$

Theorem 1.3.2. Suppose that the system (1.3.8) is such that the conditions of theorem 1.3.1 are met. Then x^* is the global attractor, that is, for an arbitrary solution (1.3.8) $x(t)$ the following is fulfilled:

$$\lim_{t\to\infty} x_i(t) = x_i^*, i = \overline{1,n} \tag{1.3.11}$$

The proof is given in Appendix A.1**.**

Evaluation of model parameters. When modeling biosystems using equations of type (1.3.8), the problem arises of estimating the parameters of the model and choosing the nucleus K. Consider the scalar equation:

$$\frac{dx(t)}{dt} = x(t)(b + c\int_{-\infty}^{t-y(t)} k(t-s)x(s)ds), t > 0 \tag{1.3.12}$$

Here, in contrast to (1.3.8), the function is introduced $y(t)$, and the aging of individuals of the population is considered "infinitely long":

$$\begin{aligned} &z(t) = -\infty, \\ &y(t) > 0, t > 0 \end{aligned} \tag{1.3.13}$$

The function $y(t)$ has the following biological content: $y(t)$ indicates the age of maturation of a particular population. So, for example, in [106] $y(t)$ as selected $y(t) = \tau_m$.

Suppose that the function $y(t) > 0$ exists

$$\inf_{t>0} y(t) = y_*.$$

As a function of the nucleus $k(s)$, we choose a function that is a generalization of the density of the Gamma distribution to equation (1.3.12):

$$g(s)=\begin{cases} 0, s \le y_*, \\ \dfrac{a^{m+1}}{\Gamma(m+1)}(s-y_*)^m e^{(s-y_*)}, s > y_* \end{cases} \tag{1.3.14}$$

When constructing models of the type (1.3.12), they deal with a variation series $\tau_1, \tau_2, ..., \tau_n$ - the implementation of a random variable τ - the value of maturation for representatives of the population.

Lemma 1.3.3. Estimates of the values of the Gamma distribution parameters (1.3.14) can be found according to the formulas:

$$a=\frac{\overset{\wedge}{\tau}}{\hat{\hat{\tau}}}, \tag{1.3.15}$$

$$m=\frac{(\hat{\tau})^2}{\hat{\hat{\tau}}}-1 \tag{1.3.16}$$

Here $\hat{\tau}$ is the unbiased mean, $\hat{\hat{\tau}}$ is the sample variance.

The proof is given in Appendix A.1.

In fact, grades (1.3.15); (1.3.16) are quite rough and can only be used as initial approximations of the real values of the distribution parameters. Better values of the distribution parameters can be obtained when we have experimental data on the density function of the ripening period $g(t), t > 0$.

Below is one of the ways to construct experimental values $g(t)$.

In real medical research, the entire population is studied using the example of some selected experimental specimens, which are called marked (for example, marked cells in microbiology).

Let's designate through $N(t)(0 \le N(t) \le 1)$ the proportion of individuals noticed that are in adulthood at a point in time t.

Lemma 1.3.4. Suppose that:

a) The mortality of individuals of the population over time v is distributed according to the density function:

$$f(v)=\begin{cases}\alpha e^{-\alpha v}, v\geq 0, \alpha>0, -\textit{константа}\\ 0, v<0\end{cases} \tag{1.3.17}$$

b) the function $N(t)$ is differentiable at $t\geq 0$.

Then the density function $g(t)$ satisfies equality:

$$g(t)=\alpha N(t)+N'(t). \tag{1.3.18}$$

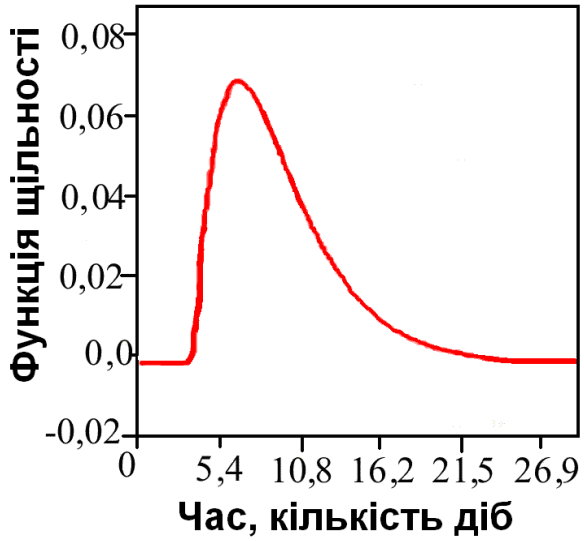
The proof is given in Appendix A.1**.**

Comments. In real-world calculations based on (1.3.18), $N'(t)$ an approximation should be used instead.

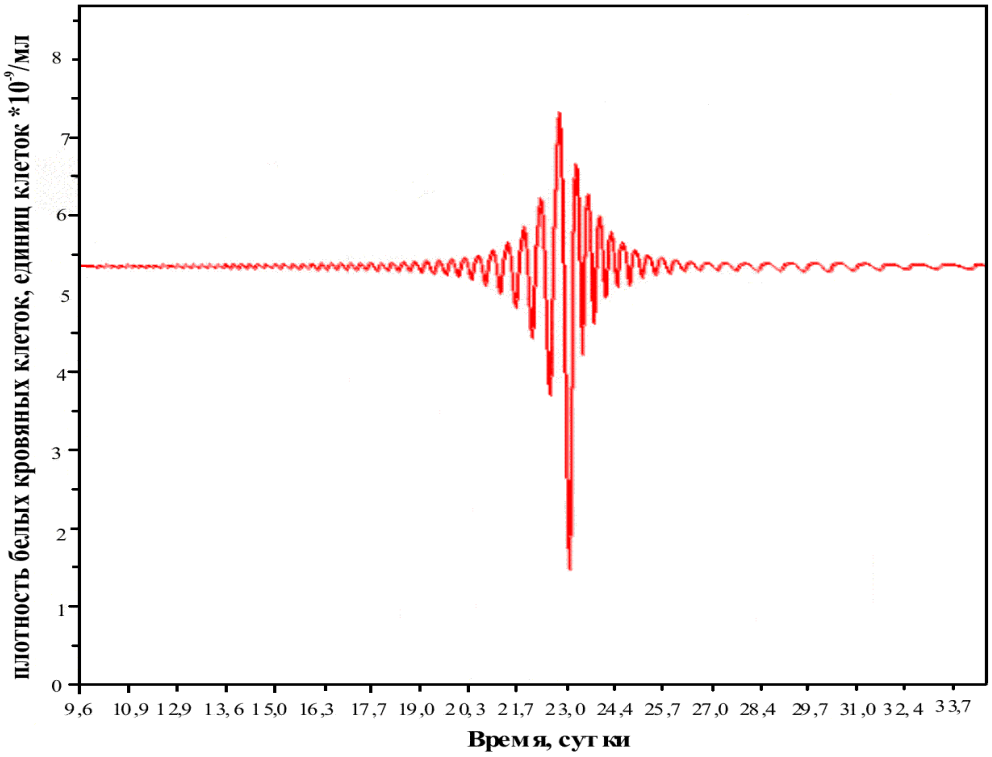
Results of numerical modeling. Let us consider one applied problem based on equation (1.3.12), which describes the production of white blood cells [23]. Blood cells (including white cells) are produced by a small population of hematopoietic stem cells [106] in the bone marrow, where they are until maturation. Further, mature cells enter the circulatory system and themselves with the help of a factor that stimulates granulocyte colonies (G-CSF) affect the production of new white blood cells [23].

Let in equation (1.3.12) $x(t)$ - the density of white blood cells involved in blood circulation (units of cells / ml of blood), $-b$ - the rate of disappearance (death) of circulating white blood cells (doba-1), c - the probable rate of production of precursors of white blood cells in the bone marrow (doba-1), $y(t)\equiv\tau_m$ - the maturation time of white blood cells (doba).

When calculating the parameter b, the formula $b = -\frac{\ln 2}{t_{1/2}}$ [23] was used, where $t_{1/2}$ is the time (number of days) of the "half-life" of the population of white blood cells. Note that the experimental data were obtained in the course of the research "Structural and functional justification of magnetolaser exposure for the prevention and correction of colon lesions" (State Registration No. 0101U001312). Figure 1.3.1 shows the results of modeling this problem for the patient at the values of the parameters $b = -2$, $c = 8.1$, $\phi(t) \equiv 10^6$. At the same time, on the basis of experimental data and formulas (1.3.15), (1.3.16), the following values of gamma distribution parameters were established: $\alpha = 0.36$, $m = 1.15$, $\tau_m = 3.48$. Simulation shows that this value of the probable rate of production of white blood cell precursors is insufficient to maintain their density at a constant level. A further increase in the value c leads to a constant level, which corresponds to a healthy state of the body.



(a)



(b)

Fig.1.3.1. Modeling the production of white blood cells using equation (1.3.12):

a) the established type of density function (1.3.18);

b) numerical solution of equation (1.3.12).

1.4. Construction of a generalized model of Gompertz dynamics

Gompertz dynamics in the most general interpretation means dynamics that are exponential at small moments of time and go to some asymptotic level at large moments of time [124].

The simplest model of Gompertz (proposed by B. Gompertz (1779-1865)) is represented by the equation:

$$\frac{dN(t)}{dt} = r\ln\left(\frac{K}{N(t)}\right)N(t), \qquad (1.4.1)$$

the solution of which is the Gompertz function:

$$N(t) = Ke^{-ce^{-rt}} \text{ where } c \text{ - some became.} \qquad (1.4.2)$$

Gompertz's models have found practical justification in oncology when describing the growth of a cancerous tumor. To do this, the following considerations should be taken into account [124]. Exponential growth is the simplest possible increase in the number of cells, corresponding to cell division, which occurs at regular intervals. Exponential growth cannot continue indefinitely. When the size of the tumor is a few percent of the size of the host (the corresponding organ), the host cannot fully support the tumor. to reach some asymptotic level.

Experimental confirmation that the Gompertz dynamics is valid for tumors was the work [113].

The American Cancer Society's Manual of Clinical Oncology [202] provides the following interpretation of tumor growth during treatment in terms of the Gompertz model.

"When cancer is found in a patient, the size of the tumor lies high in the growth phase of the Gompertz curve and therefore grows relatively slowly. By destroying the tumor by surgical removal or radiotherapy, we transfer the residual tumor to the initial phase of the Gompertz curve with faster growth, which is more sensitive to chemotherapy. Intensive chemotherapy is given long after surgery

with the hope of eradicating all residual cancer cells. Treatment continues until toxicity limits are reached and stopped."

A review of works on experimental confirmation of the adequacy of Gompertz dynamics in medicine is given in [124].

The construction of the model of this work will be based on the following biological interpretation [202].

A tumor is made up of three types of cells: proliferating cells, clonogenic cells, and end cells. t $L_P(t)$, actively share. Clonogenic cells, denoted their number by $L_C(t)$, are cancer cells at rest (in the phase G_0 of the cell division cycle). Under certain stimulation, clonogenic cells can actively begin to divide, becoming proliferating, or they can turn into terminal cells. Therefore, the goal of therapy is to convert proliferating and clonogenic cells into terminal cells.

The therapy considered in the model consists in the use m of cytotoxic agents (which may include chemotherapy drugs, radiotherapy). In terms of resistance to cytotoxic agents, populations of proliferating and clonogenic cells are divided into $2^m = M$ subpopulations, the numbers of which will be denoted by $L_{P_i}(t)$, $i = \overline{1,M}$, $L_{C_i}(t)$, $i = \overline{1,M}$ respectively.

For example, in the case when two cytotoxic agents A and B, the proliferating cells are divided into cells:

$L_{P_1}(t)$ - have no resistance to either to Aor to B;

$L_{P_2}(t)$ - resistant only to A;

$L_{P_3}(t)$ - resistant only to B;

$L_{P_4}(t)$ - resistance to and $A$to B.

The presented $2M$-compartment model of the interaction of cancer cell subpopulations is a generalization to M the -dimensional case of the model of work [118], where 2 cytotoxic agents were considered.

The model assumes that the rate of cancer development is subject to the Gompertz dynamics. To do this, the cancer spread function is introduced:

$$G_i\left(L_{P_1}(t),...,L_{P_M}(t),L_{C_1}(t),...,L_{C_M}(t)\right)=$$

$$=G\left(L_{P_1}(t),...,L_{P_M}(t),L_{C_1}(t),...,L_{C_M}(t)\right)=\alpha_L\ln\left(\frac{\theta_L}{\sum_{i=1}^{M}\left[L_{P_i}(t)+L_{C_i}(t)\right]}\right).$$

(1.4.3)

Here α_L is the rate of cancer growth, θ_L is the vital capacity of proliferating and clonogenic cells (i.e., their largest total population size).

Thus, we arrive at the equations to describe cancer cell populations:

$$\begin{aligned}\frac{dL_{P_i}(t)}{dt}&=\left[\left\{1-\alpha_i-\sum_{s=1}^{M}\left(\mu_{P_i,P_s}+\mu_{P_i,C_s}\right)\right\}L_{P_i}(t)+\sum_{s=1}^{M}\mu_{P_s,P_i}L_{P_s}(t)\right]G_i+\\&+\beta_i L_{C_i}(t)-\delta_{P_i}L_{P_i}(t)-\sum_{k=1}^{m}\left(\kappa_{P_i,k}+\sum_{s=1}^{M}\mu_{P_i,P_s,k}\right)c_k(t)L_{P_i}(t)+\\&+\sum_{k=1}^{m}\left(\sum_{s=1}^{M}\mu_{P_s,P_i,k}c_k(t)L_{P_s}(t)+\gamma_{C_i,P_i,k}c_k(t)L_{C_i}(t)\right),\quad i=\overline{1,M}.\end{aligned}$$

(1.4.4)

$$\begin{aligned}\frac{dL_{C_i}(t)}{dt}&=\left[\alpha_i L_{P_i}(t)+\sum_{s=1}^{M}\mu_{P_s,C_i}L_{P_s}(t)\right]G_i-\\&-\beta_i L_{C_i}(t)-\delta_{C_i}L_{C_i}(t)-\sum_{k=1}^{m}\left(\kappa_{C_i,k}+\gamma_{C_i,P_i,k}\right)c_k(t)L_{C_i}(t),\quad i=\overline{1,M}.\end{aligned}$$

(1.4.5)

Here $L_{P_i}(t),L_{C_i}(t),i=\overline{1,M}$ are the generalized solutions of the system on the segment (t_0,T). All the following parameters of the model are dependent on $L_{P_1}(t),...,L_{P_M}(t),L_{C_1}(t),...,L_{C_M}(t),t$.

Namely, α_i the rate that indicates the proportion of cells of the proliferating subpopulation P_i that after mitosis become clonogenic, i.e. pass to the subpopulation C_i; respectively, the $(1-\alpha_i)$ proportion of cells of the population P_i that remain in the same population; β_i - indicates the probability with which clonogenic cells of the population, C_i when appropriately stimulated, become proliferating and pass into the population P_i; $\delta_{P_i}, \delta_{C_i}$ - mortality in populations P_i and C_i, accordingly, due to natural death and transition of cells to the compartment of end cells (vascular and endothelial cells); $\kappa_{P_i,k}, \kappa_{C_i,k}$ - the probability of cell death of populations P_i and C_i , accordingly, due to the use of a cytotoxic agent c_k; $\gamma_{C_i,P_i,k}$ - the rate of transition of clonogenic cells of the population C_i into cells P_i due to the use of a cytotoxic agent c_k that caused losses in the population P_i, which are replenished to support cancer growth; $\mu_{P_s,P_i}, \mu_{P_s,C_i}$ - the probability of mutations leading to the transition from populations P_s B P_i and C P_s to B C_i , respectively; $\mu_{P_s,P_i,k}$ - the rate of acquired resistance to the chemother's drug, which appears in the presence of the agent c_k and leads to the transition of the cell from population P_s to population P_i; functions $c_k(t)$ $k=\overline{1,m}$, - piece-steel on (t_0,T) a single species, i.e. $c_k=1$ in the case of the use of k the -th agent and $c_k=0$ in its absence.

The model considers n populations of normal cells, the abundances of which at a time t are denoted by $N_i(t), i=\overline{1,n}$. The following equations are true:

$$\begin{aligned}\frac{dN_i(t)}{dt} &= \lambda_i N_i(t)\ln\frac{\theta_i}{N_i(t)} - \sum_{k=1}^{m}\kappa_{N_i,k}c_k(t)N_i(t) - \\ &-\sum_{s=1}^{M}\sigma_{P_s,N_i}L_{P_s}(t)N_i(t) - \sum_{s=1}^{M}\sigma_{C_s,N_i}L_{C_s}(t)N_i(t),\end{aligned} \tag{1.4.6}$$

where $N_i(t)$ are the generalized solutions on the segment $[t_0,T]$. Here λ_i is the population growth rate N_i; θ_i - the usual size i of the population of normal cells; $\kappa_{N_i,k}$ - the likelihood of death of population cells N_i due to the use of a cytotoxic agent c_k; σ_{P_s,N_i} and σ_{C_s,N_i} - the coefficients of loss in the population N_i due to the damaging effect of the population P_s and C_s, respectively.

The following initial conditions are put forward:

$$L_{P_1}(t_0)=1, L_{P_2}(t_0)=0,..., L_{P_M}(t_0)=0, \tag{1.4.7}$$

$$L_{C_i}(t_0)=0, i=\overline{1,M}, \tag{1.4.8}$$

$$N_i(t_0)=N_{i,0}, i=\overline{1,n}. \tag{1.4.9}$$

The initial conditions (1.4.7), (1.4.8) indicate that the treatment of cancer that began to grow in time t_0 from one proliferating cell from the population P_1 is considered - there is no resistance to any of the agents.

Phase limits of "toxicity" are considered:

$$N_i(t)\geq N_i^-, i=\overline{1,n}. \tag{1.4.10}$$

In this case, for the minimum allowable level N_i^-, an inequality is fulfilled:

$$0<N_i^-<N_{i,0}\leq\theta_i, i=\overline{1,n}. \tag{1.4.11}$$

Preferably, to check the toxicity of treatment, the number of white blood cells is determined, which is indirectly dependent on the bone marrow cells that produce them [106].

Let's denote through U - the set of permissible controls $c_k(t), k=\overline{1,m}$. In this case:

$$U=\left\{\begin{matrix}\left(u_1(t),...,u_m(t)\right), t\in[t_0,T]: u_i \text{ має скінченне число точок розриву} \\ \text{на } [t_0,T],\ 0\le u_i(t)\le 1, i=\overline{1,m}\end{matrix}\right\}$$

Let Φ be the set of allowable trajectories (1.4.4)-(1.4.10) corresponding to the set U. At the same time,

$$\Phi\subset\left\{\left(\phi_1(t),...,\phi_{2M+n}(t)\right): \phi_i(t)\in C^1[t_0,T], i=\overline{1,2M+n}\right\}.$$

When carrying out treatment, the following goals are pursued [118].

Goal 1. Put the disease into remission (that is, reduce the number of cancer cells). Often this needs to be done as soon as possible.

Goal 2. Maximize the patient's life expectancy while guaranteeing the "quality of life".

Let's denote after T - the final moment of time, L_D - the total size of cancer cell populations, which corresponds to the death of the patient. Then, when carrying out treatment with goal 1, cases should be considered.

a) T is a fixed moment in time. You need to find:

$$J_1\left(L_{P_i}(t), L_{C_i}(t), N_j(t), c_k(t)\right)=\sum_{i=1}^{M}\left[L_{P_i}(T)+L_{C_i}(T)\right]\to\inf_{\Phi\times U} \qquad (1.4.12)$$

b) Final conditions are given:

$$L_{P_i}(T)=L_{P_i,T},\quad L_{C_i}(T)=L_{C_i,T},\quad i=\overline{1,M} \qquad (1.4.13)$$

Need to find:

$$J_2\left(L_{P_i}(t), L_{C_i}(t), N_j(t), c_k(t)\right) = T \to \inf_{\Phi \times U} \tag{1.4.14}$$

When carrying out treatment for purpose 2, cases should be considered.

a) when a condition is given at the right end:

$$\sum_{i=1}^{M}\left[L_{P_i}(T) + L_{C_i}(T)\right] = L_D \tag{1.4.15}$$

You should find:

$$J_3\left(L_{P_i}(t), L_{C_i}(t), N_j(t), c_k(t)\right) = -T \to \inf_{\Phi \times U} \tag{1.4.16}$$

b) under the given condition (1.4.15) it is necessary to find:

$$J_4\left(L_{P_i}(t), L_{C_i}(t), N_j(t), c_k(t)\right) = -\int_{t_0}^{T}\sum_{i=1}^{n}\left(N_i(t) - N_i^-\right)dt \to \inf_{\Phi \times U} \tag{1.4.17}$$

So, combining the quality criteria (1.4.12), (1.4.14), (1.4.16), (1.4.17) with (1.4.4)-(1.4.10), we come to the formulation of the corresponding tasks of optimal control. Note that it is also possible to consider the relevant combinations of quality criteria (1.4.12), (1.4.14), (1.4.16), (1.4.17).

Consider the partial case of the model (1.4.4)-(1.4.10) when such assumptions are made.

1. The division of populations into subpopulations of proliferating P_i and clonogenic C_i cells is not taken into account . It follows that $\alpha_i = 0, \gamma_{C_i,P_i k} = 0, i = \overline{1,M}, k = \overline{1,m}$. Let us denote the number i of the th population of tumor cells, which has the same properties to a set of cytotoxic agents, through $L_i(t),\ i = \overline{1,M}$.

2. Mutations that occur in populations both arbitrarily (i.e., $\mu_{P_i,P_s} = 0, \mu_{P_i,C_s} = 0, i \neq s$ and due to the action k of a cytotoxic agent (i.e $\mu_{P_i,P_s,k} = 0, \mu_{P_i,C_s,k} = 0, i \neq s, k = \overline{1,m}.,$) are not taken into account.

3. Functions (1.4.3) $G_i\left(L_1(t),...,L_M(t)\right),\ i = \overline{1,M}$ form:

$$G_i\left(L_i(t)\right) = \alpha_L \ln \frac{\theta_{L_i}}{L_i(t)},$$

where θ_{L_i} is the vital capacity i of the population of tumor cells.

4. It is assumed that tumor cells do not directly have a deterrent effect on normal cells, i.e. $\sigma_{P_s,N_i} = 0, \sigma_{C_s,N_i} = 0, s = \overline{1,M}, i = \overline{1,n}$.

5. The natural mortality of tumor cells is not considered, i.e. $\delta_{P_i} = \delta_{C_i} = 0, i = \overline{1,M}$.

In this case, we come to a system of differential equations:

$$\frac{dL_i(t)}{dt} = L_i(t)\left[-\sum_{k=1}^{m} \kappa_{L_i,k} c_k(t) + \alpha_L \ln \frac{\theta_{L_i}}{L_i(t)}\right],\ i = \overline{1,M} \qquad (1.4.18)$$

$$\frac{dN_j(t)}{dt} = N_j(t)\left[-\sum_{k=1}^{m} \kappa_{N_j,k} c_k(t) + \lambda_j \ln \frac{\theta_j}{N_j(t)}\right], \qquad i = \overline{1,n} \qquad (1.4.19)$$

with initial conditions:

$$L_1(t_0)=1, L_2(t_0)=0,..., L_M(t_0)=0, \tag{1.4.20}$$

$$N_j(t_0)=N_{j,0}, j=\overline{1,n}. \tag{1.4.21}$$

Here $L_i(t), i=\overline{1,M}, N_j(t), j=\overline{1,n}$ are piecewise continuous functions on the segment $[t_0,T]$.

The study of the controllability of the system (1.4.18)-(1.4.21) is reduced to the problem that is considered in subsection V.1.

1.5. Additionality and existence of solutions to the generalized model of Gompertz dynamics

The model is considered:

$$\frac{d\eta_i(t)}{dt}=\sum_{s=1}^{K}a_{is}\eta_s(t)\ln\frac{\theta}{\sum_{s=1}^{K}\eta_s(t)}+\sum_{s=1}^{K}b_{is}\eta_s(t), \quad i=\overline{1,K},$$

$$\frac{dN_j(t)}{dt}=N_j(t)\left\{\sum_{s=1}^{n}\lambda_{js}\ln\frac{\theta_s}{N_s(t)}-\sum_{s=1}^{K}\sigma_{sj}\eta_s(t)\right\}, \quad j=\overline{1,n},$$

$$t\in[t_0,\infty). \tag{1.5.1}$$

with initial conditions:

$$\eta_i(t_0)=\eta_{i,0}, i=\overline{1,K}, \quad N_j(t_0)=N_{j,0}, j=\overline{1,n}, \tag{1.5.2}$$

which satisfy:

$$\sum_{i=1}^{K}\eta_{i,0}<\theta, \quad N_{j,0}>0, j=\overline{1,n}. \tag{1.5.3}$$

The models of Gompertz dynamics considered in the paper can be reduced to the model (1.5.1)-(1.5.3).

This subsection will establish the conditions under which there are positive solutions (1.5.1)-(1.5.3) satisfying:

$$\eta(t)=\left(\eta_1(t),...,\eta_K(t)\right)\in S_\theta^1[t_0,\infty),\quad N(t)=\left(N_1(t),...,N_n(t)\right)\in C^1[t_0\infty),\tag{1.5.4}$$

where $S_\theta^1[t_0,\infty)=\left\{\left(\phi_1(t),...,\phi_K(t)\right)\in C^1[t_0,\infty):\sum_{i=1}^{K}\phi_i(t)<\theta,t\in[t_0,\infty)\right\}$.

Along with equations (1.5.1), their integral analogues are considered:

$$\eta_i(t)=\eta_{i,0}+\int_{t_0}^{t}\left[\sum_{s=1}^{K}a_{is}\eta_s(t)\ln\frac{\theta}{\sum_{s=1}^{K}\eta_s(t)}+\sum_{s=1}^{K}b_{is}\eta_s(t)\right]dt=\mathrm{A}_{\eta_i}\left(\eta(t)\right),\quad i=\overline{1,K}$$

(1.5.5)

$$N_j(t)=N_{j,0}+\int_{t_0}^{t}N_j(t)\left\{\sum_{s=1}^{n}\lambda_{js}\ln\frac{\theta_s}{N_s(t)}-\sum_{s=1}^{K}\sigma_{sj}\eta_s(t)\right\}dt=\mathrm{A}_{N_j}\left(\eta(t),N(t)\right),\quad j=\overline{1,n}$$

Lemma 1.5.1. Let:

1) the initial conditions of the system (1.5.1) satisfy the inequality (1.5.3);

2) condition (A0) is fulfilled

for an arbitrary vector $\xi\in R^K:0<\sum_{i=1}^{K}\xi_i<\theta$

$$\sum_{i,s=1}^{K}a_{is}\xi_s\frac{\sum_{s=1}^{K}\xi_s}{\theta}+\sum_{i,s=1}^{K}\left(b_{is}-a_{is}\right)\xi_s>0,\quad a_{is}>0,\quad i,s=\overline{1,K}.\tag{1.5.6}$$

Then any solution (1.5.1), (1.5.2) for an arbitrary one $t\in(t_0,\infty)$ satisfies the inequalities:

$$\sum_{i=1}^{K}\eta_i(t)>0, \tag{1.5.7}$$

$$N_j(t)>0,\ j=\overline{1,n} \tag{1.5.8}$$

The proof is given in Appendix A.1.

Theorem 1.5.1. Let the conditions of lemma 1.5.1 be met. Then there is a single solution to the problem (1.5.1)-(1.5.3).

The proof is given in Appendix A.1**.**

Consequence 1.5.1. Let the conditions of theorem 1.5.1 be fulfilled and condition (A1) is satisfied:

either the matrix $B=\{b_{is}\}_{i,s=\overline{1,K}}$ is degenerate, or the matrix B is not degenerate and an $\xi=(\xi_1,...,\xi_K)\in R_+^K:\sum_{i=1}^{K}\xi_i\geq\theta$ inequality is fulfilled for an arbitrary vector:

$$\theta\frac{\sum_{i,s=1}^{K}a_{is}\xi_s}{\sum_{s=1}^{K}\xi_s}+\sum_{i,s=1}^{K}(b_{is}-a_{is})\xi_s<0,\quad a_{is}\geq 0,i,s=\overline{1,K}. \tag{1.5.9}$$

Then there is a single solution (1.5.1)-(1.5.3) such that for arbitrary there $t\in[t_0,\infty)$ is:

$$\sum_{i=1}^{K}\eta_i(t)<\theta. \tag{1.5.10}$$

The proof is given in Appendix A.1.

Consequence 1.5.2. When the conditions of theorem 1.5.1 are met, the operators $\mathrm{A}_{\eta_i}(\eta(t)),\quad i=\overline{1,K}$ and $\mathrm{A}_{N_j}(\eta(t),N(t)),\quad j=\overline{1,n}$, which are defined

on the corresponding Banach spaces, satisfy the principle of compressive mappings, and their fixed points are solutions to the problem (1.5.1)-(1.5.3), which satisfy the conditions (1.5.7), (1.5.8)

1.6. Generalized model of antitumor immunity

Immunity is a surveillance system, the main function of which is to control the processes of proliferation of cell differentiation and destruction of mutant cells [23]. The achievements of immunology over the past 30 years have fully confirmed the idea of F. Burnett, expressed for the first time in 1959, that antimicrobial action is only a partial manifestation of immunity. Thus, infectious immunology became the basis for the emergence of a new area of scientific knowledge - non-infectious immunology, One of the important areas of which is the development of antitumor immunity.

Such immunity depends on the cause of the tumor (viruses, carcinogenic chemicals, "spontaneous" tumors). Immunity is specific to the viruses that induced the tumor (DNA or RNA-containing viruses). It occurs a few days or even hours after the introduction of viruses and persists for months.

Immunity to tumors indicated by carcinogens is weaker than immunity to virus-induced tumors, and even weaker immunity to tumor cells that "spontaneously" arise [76].

The model under consideration is based on the following simplified view of antitumor immunity [23].

The immune system develops an immune response to a growing tumor (cellular, thanks to cytotoxic T-lymphocytes, and humoral, the factors of which are antibodies, for example, specific IgG and IgM). Immune reactions are induced by a specific tumor antigen, which is found in different parts of the tumor cell (mainly on the surface).

In the following model, the following assumptions are made:

1. Populations of cancer cells, antibodies, plasma cells are heterogeneous.

2. Changes in the number of cancer cell populations are subject to the laws of generalized Gompertz dynamics.

3. The immune response is induced by tumor antigen and specific antibodies.

4. The concentration of tumor antigens at a time t is proportional to the number of tumor cells of the corresponding pool.

5. Cancer cells have a deterrent effect on the growth of the antibody population.

6. The toxicity of treatment is determined by the concentration of bone marrow cells, which is measured through bone mineral density.

7. Changes in bone mineral density are subject to logistical dynamics.

Thus, we arrive at the following system of differential equations:

$$\begin{aligned}\frac{dL_{P_i}(t)}{dt} &= \left[\left\{1-\alpha_i-\sum_{s=1}^{M}\left(\mu_{P_i,P_s}+\mu_{P_i,C_s}\right)\right\}L_{P_i}(t)+\sum_{s=1}^{M}\mu_{P_s,P_i}L_{P_s}(t)\right]G_i+\\ &+\beta_i L_{C_i}(t)-\delta_{P_i}L_{P_i}(t)-\sum_{k=1}^{m}\left(\kappa_{P_i,k}+\sum_{s=1}^{M}\mu_{P_i,P_s,k}\right)c_k(t)L_{P_i}(t)+\\ &+\sum_{k=1}^{m}\left(\sum_{s=1}^{M}\mu_{P_s,P_i,k}c_k(t)L_{P_s}(t)+\gamma_{C_i,P_i,k}c_k(t)L_{C_i}(t)\right),\quad i=\overline{1,M}.\end{aligned} \tag{1.6.1}$$

$$\begin{aligned}\frac{dL_{C_i}(t)}{dt} &= \left[\alpha_i L_{P_i}(t)+\sum_{s=1}^{M}\mu_{P_s,C_i}L_{P_s}(t)\right]G_i-\\ &-\beta_i L_{C_i}(t)-\delta_{C_i}L_{C_i}(t)-\sum_{k=1}^{m}\left(\kappa_{C_i,k}+\gamma_{C_i,P_i,k}\right)c_k(t)L_{C_i}(t),\quad i=\overline{1,M}.\end{aligned} \tag{1.6.2}$$

$$\frac{dC_{P_i}(t)}{dt} = \xi(m)\alpha_{P_i} L_{P_i}\left(t-\tau_{C_{P_i}}\right) F_{P_i}\left(t-\tau_{C_{P_i}}\right) - \mu_{C_{P_i}}\left(C_{P_i} - C_{P_i,0}\right) + \\ + b_{C_{P_i}}\rho(t) - \sum_{k=1}^{m}\beta_{C_{P_i},k} c_k(t) C_{P_i}(t),\ i=\overline{1,M} \tag{1.6.3}$$

$$\frac{dC_{C_i}(t)}{dt} = \xi(m)\alpha_{C_i} L_{C_i}\left(t-\tau_{C_{C_i}}\right) F_{P_i}\left(t-\tau_{C_{C_i}}\right) - \mu_{C_{C_i}}\left(C_{C_i} - C_{C_i,0}\right) + \\ + b_{C_{C_i}}\rho(t) - \sum_{k=1}^{m}\beta_{C_{C_i},k} c_k(t) C_{C_i}(t),\ i=\overline{1,M} \tag{1.6.4}$$

$$\frac{dF_{P_i}(t)}{dt} = b_{f_{P_i}} C_{P_i} - \left(\mu_{f_{P_i}} + \eta_{P_i}\gamma_{L_{P_i}} L_{P_i}(t)\right) F_{P_i}(t),\ i=\overline{1,M}, \tag{1.6.5}$$

$$\frac{dF_{C_i}(t)}{dt} = b_{f_{C_i}} C_{C_i} - \left(\mu_{f_{C_i}} + \eta_{C_i}\gamma_{L_{C_i}} L_{C_i}(t)\right) F_{C_i}(t),\ i=\overline{1,M} \tag{1.6.6}$$

$$\frac{dm(t)}{dt} = \sum_{i=1}^{M}\sigma_{P_i} L_{P_i}(t) + \sum_{i=1}^{M}\sigma_{C_i} L_{C_i}(t) - \mu_m m(t), \tag{1.6.7}$$

$$\frac{d\rho(t)}{dt} = b_\rho \rho(t)\left(\overline{\rho} - \rho(t)\right) - \\ - \sum_{i=1}^{M} d_{P_i} C_{P_i} - \sum_{i=1}^{M} d_{C_i} C_{C_i} - \sum_{k=1}^{m}\beta_{\rho,k} c_k(t)\rho(t) \tag{1.6.8}$$

Here, equations (1.6.1) and (1.6.2) fully coincide with their counterparts from subsection 1.4 and use the same designations for subpopulations of cancer cells; $C_{P_i}(t)$ and $C_{C_i}(t)$, $i=\overline{1,M}$ - concentrations of plasma cells that produce antibodies, specific to P_i and C_i respectively, the concentrations of which we

denote through $F_{P_i}(t)$ and $F_{C_i}(t)$; $m(t)$ - the degree of damage to the organ, $\rho(t)$ - the mineral density of bone tissue.

Next, we will give the values of the coefficients of the model:

$\alpha_{P_i}, \alpha_{C_i}$ - coefficients that determine the likelihood of an antigen-antibody meeting; $\mu_{C_{P_i}}, \mu_{C_{C_i}}$ - coefficients inverse of the lifetime of plasma cells; $b_{f_{P_i}}, b_{f_{C_i}}$ - the rate of antibody production by one plasma cell; $\mu_{f_{P_i}}, \mu_{f_{C_i}}$ - coefficients inversely proportional to the time of decay of antibodies; η_{P_i}, η_{C_i} - the number of specific antibodies required to neutralize one antigen; $\sigma_{P_i}, \sigma_{C_i}$ - coefficients that determine the rate of cell death due to the damaging effect of antigens; μ_m - a coefficient that takes into account the speed of recovery of the damaged organ; $\tau_{C_{P_i}}, \tau_{C_{C_i}}$ - delay phases (the time during which the formation of a cascade of plasma cells is carried out); $b_{C_{P_i}}, b_{C_{C_i}}$ - the rate of production of plasma cells per unit of bone density $\beta_{\rho,k}$ - the coefficients of reducing the mineral density of bone tissue due to the toxic effect k of the cytotoxic agent; $\xi(m)$ - continuous non-increasing function ($0 \le \xi(m) \le 1$), which characterizes a violation of the normal functioning of the immune system due to significant damage to the target organ.

The listed parameters are positive and are specific both for the type of antigen, and for the organ, and for a specific organism.

At the same time,

$L_{P_i}(t), L_{C_i}(t), C_{P_i}(t), C_{C_i}(t), F_{P_i}(t), F_{C_i}(t), m(t), \rho(t) \in C^1[t_0, \infty)$, $i = \overline{1, M}$,

a $c_k(t), k = \overline{1, m}$ - piecewise continuous functions with values $0 \le c(t) \le 1$ (such an assumption can be made after appropriate rationing).

Continuous initial conditions are given for $t \in [t_0 - \tau^*, t_0]$, $\tau^* = \max\limits_{i=1,M} \left\{ \tau_{C_{P_i}}, \tau_{C_{C_i}} \right\}$:

$$L_{P_i}(t)=L_{P_i,0}(t), L_{C_i}(t)=L_{C_i,0}(t),\ C_{P_i}(t)=C_{P_i,0}(t), C_{P_i}(t)=C_{P_i,0}(t),$$
$$F_{P_i}(t)=F_{P_i,0}(t),\ F_{C_i}(t)=F_{C_i,0}(t), m(t)=m_0(t),\ \rho(t)=\rho_0(t) \quad (1.6.9)$$

In the future, mathematical methods for system analysis of models for which (1.6.1)-(1.6.9) are generalizations will be developed. Therefore, in our work, we will often refer to the model just given as a generalized model of the pathological process.

1.7. Simplified model of antitumor immunity

In the following simplified model, the following assumptions are made:

1. Populations of cancer cells, antibodies, plasma cells are homogeneous.

2. Changes in the size of the population of cancer cells are subject to the laws of Gompertz dynamics.

3. The immune response is induced by tumor antigen and antibodies of the same species.

4. The concentration of tumor antigens at a time t is proportional to the number of tumor cells $L(t)$.

5. Cancer cells have a deterrent effect on the growth of the antibody population.

6. The toxicity of treatment is determined by the concentration of bone marrow cells, which is measured through bone mineral density.

7. Changes in bone mineral density are subject to logistical dynamics.

Thus, in the absence of any cytotoxic agent, we arrive at the following system of differential equations:

$$\frac{dL(t)}{dt} = \alpha_L L(t) \ln \frac{\theta_L}{L(t)} - \gamma_L F(t) L(t), \quad (1.7.1)$$

$$\frac{dC(t)}{dt} = \xi(m) \alpha L(t-\tau) F(t-\tau) - \mu_C (C - C_0) + b_C \rho(t), \quad (1.7.2)$$

$$\frac{dF(t)}{dt} = b_f C - (\mu_f + \eta \gamma_L L(t)) F(t), \quad (1.7.3)$$

$$\frac{dm(t)}{dt} = \sigma L(t) - \mu_m m(t), \quad (1.7.4)$$

$$\frac{d\rho(t)}{dt} = b_\rho \rho(t) (\overline{\rho} - \rho(t)), \quad (1.7.5)$$

where $L(t)$ is the number of tumor cells, $C(t)$ - the concentration of plasma cells, $F(t)$ - the concentration of antibodies, $m(t)$ - the degree of organ damage, $\rho(t)$ - the mineral density of bone tissue. In this case $L(t), C(t), F(t), m(t), \rho(t) \in C^1[t_0, \infty)$. γ_L - the coefficient that determines the probability of neutralization (destruction) of a cancer cell by an antibody b_C is the rate of production of plasma cells per unit bone density. A description of the remaining coefficients of the model (1.7.1)-(1.7.5) is given in the previous subsection.

Continuous initial conditions are given for $t \in [t_0, -\tau, t_0]$:

$$L(t) = L_0(t), \quad C(t) = C_0(t), \quad m(t) = m_0(t), \quad \rho(t) = \rho_0(t). \quad (1.7.6)$$

When carrying out therapeutic treatment, it is additionally assumed that the cytotoxic agent (concentration $c(t)$) kills both cancerous and normal (plasma cells, bone marrow cells) cells. We believe that $c(t)$ it is a piecewise continuous

function with values $0 \le c(t) \le 1$ (such an assumption can be made after appropriate rationing).

We get a system of differential equations:

$$\frac{dL(t)}{dt} = \alpha_L L(t) \ln \frac{\theta_L}{L(t)} - -\beta_L c(t) L(t) - \gamma_L F(t) L(t), \tag{1.7.7}$$

$$\frac{dC(t)}{dt} = \xi(m) \alpha L(t-\tau) F(t-\tau) - \mu_C (C - C_0) + b_C \rho(t) - \beta_C c(t) C(t), \tag{1.7.8}$$

$$\frac{dF(t)}{dt} = b_f C - \left(\mu_f + \eta \gamma_L L(t)\right) F(t), \tag{1.7.9}$$

$$\frac{dm(t)}{dt} = \sigma L(t) - \mu_m m(t), \tag{1.7.10}$$

$$\frac{d\rho(t)}{dt} = b_\rho \rho(t) \left(\overline{\rho} - \rho(t)\right) - \beta_\rho c(t) \rho(t). \tag{1.7.11}$$

Here $L(t), C(t), F(t), m(t), \rho(t)$ are lumpwise continuously differentiable on $[t_0, \infty)$.

Example 1.7.1. With the help of a computer program, a quantitative study of the process of antitumor immunity was carried out when:

$$\alpha_L = 0.00396, \theta_L = 14, \gamma_L = 0.008, \alpha = 10^4, \mu_c = 0.5, \rho = 0.17, \mu_f = 0.17,$$
$$\eta = 10, \mu_m = 0.12, b_C = 0$$

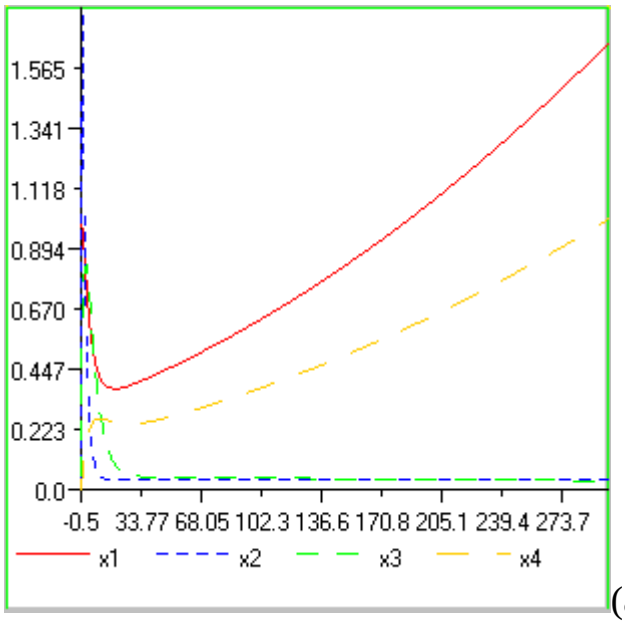
$$\xi(m) = \begin{cases} 1, m \le 0.1 \\ (1-m)/(10/9), 0.1 \le m \le 1 \end{cases}$$

If $t \in [-\tau, 0]$ the following initial conditions are true

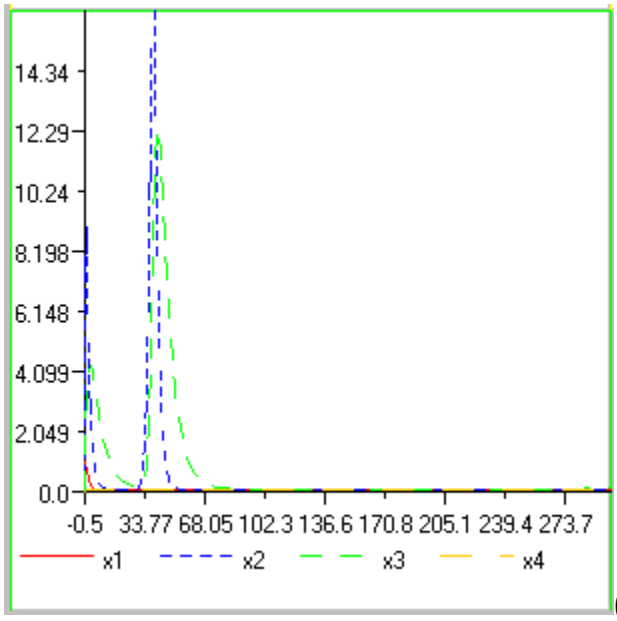
$L(t) = 1, C(t) = 1, F(t) = 1, m(t) = 0$.

The simulation carried out (Fig. 1.7.1) shows that the time of the appearance of the immune response and its effectiveness depend on the coefficient

σ, which is the rate of death of organ cells due to the inhibitory effect of tumor cells.



(a)



(b)

Fig. 1.7.1. Numerical modeling of the system (1.7.1)-(1.7.4). The graphs show: x1 - $L(t)$, x2 - $C(t)/30$, x3 - $F(t)/20$, x4 - $m(t)$.

a) $\sigma = 50$ - the immune response is insufficient;

b) $\sigma = 10$ - the immune response is sufficient and repeated;

Conclusions. 1. Thus, an algorithm of system analysis was formulated in order to study the causes and features of the dynamics of the development and course of the disease. From the whole variety of alternatives to scientific directions, a direction based on the study of the general pathological process from the point of view of the theory of dynamic systems was synthesized.

2. The results on the existence of a solution and a global attractor in the class of integro-differential equations with memory are obtained. For this purpose, the concept of a positively defined matrix nucleus relative to the memory function has been introduced. This concept is an extension of the well-known definition to the class of integro-differential equations with memory. It is shown that in the case of a positively defined kernel, there is a global attractor of the system relative to the memory function. For the applicability of this condition in real calculations, effective numerical criteria should be developed in the future.

3. The method of constructing the integral core of the scalar model based on experimental data is shown. When using the Gamma distribution density function as the nucleus, unknown parameters can be easily obtained from experimental data (for example, data on the maturation of blood cells). When searching for the nucleus in a general form, an experimental way of using the method of "labeled cells", which is widely used in immunology, is proposed [23]. This approach is simple in numerical implementation, although in practice it requires precise laboratory equipment.

4. As follows from the results of numerical modeling of equation (1.3.12) to describe the production of white blood cells, a certain rate of reproduction is required to maintain cell density at some constant level. Otherwise, certain fluctuations occur. This phenomenon has biological evidence. Among them is cyclic neutropenia, a disease in which the density of neutrophils oscillates between normal and very low values. The causes of cyclic neutropenia are: the existence of oscillations in many peripheral cellular elements, an abnormally high mortality rate within the proliferating compartment; loss of stability in the

peripheral control cycle, acting as a data between the number of mature neutrophils and the control of the rate of production of neutrophil precursors in the bone marrow [117].

5. To obtain more accurate values of estimates a and m parameters of the Gamma distribution, it is necessary to study the optimization problem, in which the values (1.3.15), (1.3.16) should be chosen as initial approximations, and the target function should be chosen:

$$\int_0^{\infty} (g(s) - g^*(s))^2 ds \to \inf_{a,m}$$

where $g(s)$ is given according to (1.3.14), and $g^*(s)$ - (1.3.18).

6. It makes sense to develop methods for constructing an estimate of the integral core of the model in a general form based on a minimax posteriori estimation in Hilbert space, which will be discussed in the next section.

7. The model of Gompertz dynamics for the case $2M$ of subpopulations of cancer and n subpopulations of normal cells is generalized. At the same time, the use m of various cytotoxic agents is considered. The formulation of optimal control problems relative to the goals of treatment is made. The conditions of existence and applicability of the solutions of the model, as well as the issue of finding equilibrium states are investigated.

8. A generalized model of describing antitumor immunity is proposed, which we will also refer to as a generalized model of the pathological process. It is based on the generalized model of dynamics of Gompertz, the model of immune defense of G.I. Marchuk, the model of bone tissue reconstruction.

These results are reflected in the monograph [185], a number of journal articles [166, 175, 177, 180, 199, 200, 201] and conference proceedings [153, 162, 172, 183, 204].