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========== TRANSLATIONS OF PUBLISHED ARTICLES ==========

A Mathematical Model for Evolution of Human Functional Disorders Influenced by Environment Factors

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Abstract. A mathematical model predicting the evolution of human functional disorders under environment influence is developed. The natural aging, regeneration processes, accumulation of damage due to abnormal substances streams and functional recovery through treatment are considered. Inflow of substances from the environment, accumulation, metabolism and elimination are described with neuro-humoral regulation. Numerical solution of differential equations based on implementation of finite difference schemes are obtained for different cases.

Key words: *mathematical modeling, evolution equations, functional disorders, environment influence.*

1. INTRODUCTION

The human body constantly interacts with the environment in its vital activity. It gets all the necessary nutrients from it and is exposed to adverse chemical, physical, biological, and other environmental factors. Over many years, negative environmental effects on human health have been growing due to increasing industrial emissions, emissions from motor transport, and noise exposure. Influence of socioeconomic factors is no less significant; in particular, the existing distribution is associated with growing work intensity for most working age people. This affects mental health and ultimately physical one as well. Poorer health results in economic losses due to premature deaths, disability and incidence with temporary loss of ability to work.

Health can be estimated with clinical, laboratory and functional investigations. They provide all the data necessary for solving a wide range of tasks, from making a decision on a relevant therapy to performing some complex specialized examinations. The aforementioned research techniques are well-developed and allow performing a comprehensive complex examination of the whole body. They are predominantly aimed at discovering qualitative functional disorders of organs and systems. Laboratory and functional diagnostics relies on reference ranges of indicators and indexes. In case indicators fall out of these reference ranges, functional disorders are not quantified; at best, some scale is provided showing levels of hazards or severity of these disorders. On the other hand, although laboratory diagnostic techniques are being developed quite rapidly, many studies remain rather labor-consuming, expensive, and time-consuming; they often require experts with some specific training but still don't establish a cause of a disease. Moreover, laboratory techniques do not make it

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possible to predict functional disorders of organs and systems in the human body but it is this task that is a priority one in health-related issues.

Knowledge on causes, factors of a specific disease and mechanisms of its progression would considerably facilitate success in diagnosing it and predicting its probable clinical course. Mathematic modeling techniques are among the most promising approaches to estimating contributions made by various factors to health disorders and establishing relevant cause-effect relations. Mathematical models are built based on analyzing regularities in interactions of organs and systems, between each other and environmental factors as well.

The human body is affected by thousands of factors. Thus, ambient air alone in a large industrial city contains approximately 400 various adverse chemicals in different combinations of their levels. Experiments performed on just twenty of them require substantial materials costs. A major advantage of mathematic modeling is an opportunity to save time and resources. Besides, use of mathematic modeling makes it possible to change or completely exclude any exposures, investigate influence of specific factors or their various combinations. Numeric experiments allow simulating exposures that are harmful for human life and health and therefore unacceptable for any full-scale experiments. Mathematical models give an opportunity not only to assess and compare functional disorders in organs and systems but also predict their functional state under exposure to various environmental factors.

Research works that address modeling of ageing processes have been published since medicine was established as a science and mathematics as a learning instrument. Historical documents mention works by Hippocrates and Aristotle that describe ageing as a phenomenon occurring due to loss of ‘natural heat’. Contemporary studies in the field received a new impulse to develop when such scientific disciplines as biophysics, biomechanics, and mathematical biology came to life.

In the late 1990s and early 2000s, works on modeling of ageing processes started to show some contradictions between old principles of creating conceptual gerontological models limited to absolutization of separate observable phenomena and some purely mathematical approaches, which were not accepted by biologists and were not of interest for them [1]. According to some scientists (V.I. Dontsov, V.N. Krut’ko and others), purely mathematical models are too theoretical, have no biological feasibility and are actually incorrect due to false initial preconditions.

At the same time, there is strong demand for working out a clear common concept of ageing and its embodiment in models able to interpret ageing of live organisms quantitatively and informatively. V.N. Dontsov points out that many elements of such models already exist in various spheres of biology. By now, more than 200 theories to explain ageing are available; this indicates not only absence of one common theory and concepts of the process or lack of knowledge on causes and essence of ageing but also frequent failure to get a proper methodological insight into the heart of the problem [2].

The model by Gompertz-Makeham is one of the first that meet the requirements to essential theories of ageing. It is quite consistent with experimental data on mortality among adults [3, 4]. By now, multiple modifications of the model have been developed; they mostly describe only natural ‘wear and tear’ of the human body [5, 6]. Models that describe a relationship between mortality and age are employed to create predictions in demography and epidemiology [7–9].

So called ‘burden’ models are used to consider adverse environmental exposures; they describe an additional component in intensity of mortality [10]. The models, which we have considered, are based on statistical data and do not cover formation and mutual influence of ongoing processes; they are not aimed at looking into the nature of analyzed phenomena.

Contemporary approaches to modeling processes of ageing require mandatory inclusion of interactions between live organisms and the environment. V.N. Krut’ko classifies

mechanisms of ageing in his studies [1, 11, 12] and highlights several of them as the most significant ones:

1) systemic ‘pollution’ of the body over time due to it being insufficiently open to the environment and ineffective excretion of metabolic wastes;

2) loss of non-renewable elements of the body at any level in its structure;

3) accumulation of lesions and deformations due to fundamental deficiency of capabilities of self-renewable structures to preserve the necessary system elements;

4) unfavorable changes in regulation.

Most models that describe mechanisms of ageing are based on formulating and solving systems of ordinary differential equations. They reflect how health disorders develop in the human body.

The homeostatic model developed by V.N. Novosel’tsev [13, 14] merits some attention among theories that concentrate on deep mechanisms of ageing. In this model, physiological ageing is associated with oxidative damage accumulated in the human body. The human body is seen as an integral system able to resist various damaging and destroying exposures. The model suggested by V.N. Novosel’tsev is a reliable instrument for predicting death and analyzing its possible scenarios. To develop the suggested concept, E.A. Mashintsov and A.E. Yakovlev developed a mathematical model to describe the body life cycle. Its key output parameters are life expectancy at birth and years of potential life lost [15, 16]. The authors limited their research to considering only several basic organs and systems (the kidneys, liver, cardiovascular and respiratory system); the model does not include a component that reflects interaction between the body and environmental factors.

Influence exerted by environmental factors was considered in the models suggested by L. Schlessinger and others [17]. They describe changes in human biological indicators associated with diseases considering environmental exposures. Equations are built based on statistical approaches and the authors highlight that even if their model relies on population data, it considers individual health with respect to anatomy, physiology, pathology and a reaction to treatment. The authors provide a detailed description of an algorithm for resolving issues associated with data identification, verification, and incompleteness. However, it seems rather difficult to use the reported data in future studies since the research does not provide values of the model parameters.

Theoretical mechanisms to explain ageing are diverse; this leads to creation of models that seem more interesting with respect to information-analytical modeling techniques rather than their practical use for solving biological or medical tasks. The information-entropy ageing model suggested by A.Sh. Avshalumov can be a good example here; it is based on an assumption that a key role in preserving viability of the human body belongs to information processes. They maintain the human body as an integral system and viability tends to be lost over time due to lower informative connectivity of the body caused by increasing entropy, an objective ongoing process within any closed system [18].

Latest studies with their focus on developing mathematic models to describe accumulation of damage in the body tend to be significantly complicated and rely on a great number of indicators. Given that, researchers are facing a serious challenge associated with identification of theoretical models. A.P. Parakhonskii explains that biomedical systems typically have very complicated dynamics of processes depending on multiple factors, which are very difficult to consider, analyze, and investigate [19]. Functional and structural identification is applied to estimate parameters in biochemical models [20]. L.I. Kalakutskii showed in his works that the former method required experimental data on how a system would behave under various initial exposures and this was rather hard to achieve when modeling processes within the biological ageing theory. On the other hand, structural identification makes it possible to establish interactions between separate components of the system within formation of reactions.

Published research works allow concluding that it is optimal to use structural identification with subsequent planning of an experiment to identify missing parameters (functional identification). The Physiome Project is used as an international information resource for such studies [21, 22]. It contains research works that focus on mathematical modeling of physiological processes. The main aim of the project is to develop a model of the human body using methods that combine biochemistry, biophysics and anatomy of cells, tissues, and organs. Such approaches give an opportunity to describe physiological processes in organs and systems in depth; however, the present stage in the project development does not set a task to describe how functional disorders accumulate in various organs or to analyze effects produced by environmental factors. Nevertheless, some physiological models already consider some exposures, for example, cigarette smoke inhalation [23] or Helicobacter Pylori infection of the gastric mucosa [24].

It is noteworthy that most publications analyzed in this study have very few or even no references to other works in the field. This is probably due to this trend in research being developed rather poorly.

Given all the aforementioned, it seems a vital issue and an actual challenge to develop a mathematical model able to predict how functional disorders would develop in the body under environmental exposures. The analyzed objects are complex and physiological processes are described with a wide range of spatial (an ion channel is 1 nanometer and the whole body is 1–2 meters) and temporal (from 1 microsecond for molecular movement to 70–80 years (10^9 seconds) of a lifetime) scopes. Therefore, the authors of the present study are developing a multi-level model to describe how the human body functions. The upper level (macro-level) is the body as a whole; the second level (meso-level) describes specific organs or systems. In its turn, each level may require creating some submodels that describe functioning of its most important sub-systems. This study focuses on developing a macro-level model, its mathematical structure, basic concepts and definitions. Since some parameters included into this macro-level model are to be established by using meso-models, the macro-level model shows only qualitative nature of the human body evolution at this stage in its development. Since the whole macro-level model in not a closed system, we had to introduce some ‘plugs’ at those sections of it where ‘inputs’ from meso-level models are to be located in future. Such ‘plugs’ are represented by data of clinical examinations averaged as per some population groups, expert evaluations, etc. Therefore, multiple specific exposures are not considered at this stage; to demonstrate how the model operates at a first approximation, we identified several basic parameters.

The model should consider individual age-specific features of the human body, systemic interactions between different organs, accumulation of functional disorders due to natural processes and environmental exposures, neural-immune-endocrine regulation and other processes that are the most significant for vital activity. It is noteworthy that though the model makes it possible to consider exposure to any environmental factor conceptually, its variant described in the present study focuses on chemical exposures. Effects produced by physical and social factors are not examined profoundly. The study concentrates on reporting and analyzing some qualitative results obtained by using the suggested model.

2. CONCEPTUAL STATEMENT

The human body is assumed to consist of finite set of organs (systems) (j = 1, 2,…., J) that are completely interrelated. Generally, the macro-model should cover the following systems: the respiratory system (lungs), digestive system, cardiovascular system, genitourinary system (kidneys), skin and subcutaneous fatty cellular tissue, musculoskeletal system, endocrine system, nervous system, immune system, and hematopoietic system.

Impaired functional abilities of the j-th organ (system) are described with damage $D_j(t)$, which is a time (age)-dependent parameter t, $D_j(t) \in [0,1]$; the $D_j = 0$ means the body is

functioning properly (ideally); $D_j = 1$ means an organ (system) is unable to perform its functions. Functionality of an organ (system) $F_j(t)$ can be identified relying on damage to them; functionality can be defined as ability of an organ (system) to perform its functions. For example, a relationship between functionality and damage can be given as $F_j(t) = (1 - D_j(t))^{n_j}$, $n_j \in R \geq 1$. The human body is a biological system; therefore, its natural property is to accumulate functional disorders over time, which may later become apparent through developing diseases.

Functional disorders may develop due to natural causes, namely, internal 'self-destruction', which occurs, as a rule, on the cellular level and reflects natural ageing of the body. Organs and systems, just as the body as a whole, are able to perform self-recovery (reparation) of lost functions.

Creation of a model that describes accumulation of functional disorders in the human body under environmental exposures is aimed at investigating interactions between organs and chemicals in blood. This calls for establishing relationships able to describe how chemicals penetrate the body from the environment. Basic ways of chemical entry include oral (through the gastrointestinal tract), inhalation (through the lungs) and percutaneous (through skin). Consequently, when modeling entry of chemicals, it is necessary to consider any damage of the respiratory system, digestive system, or skin. Chemicals are excreted (taken out of the body into the environment) through the kidneys, respiratory system, digestive system, and skin. There are two other mechanisms that can change levels of chemicals in blood, metabolism and deposition (accumulation) in various organs.

Information exchange between different organs facilitates activation of the body reserves necessary for functional compensation and neutralization of harmful exposures and their outcomes. This exchange is performed by regulatory mechanisms. Three systems in the body are responsible for the regulatory function, namely, the endocrine, nervous and immune system. These systems are closely connected to each other and their interaction is usually called the neural-immune-endocrine regulation. Any failure in the regulatory system functioning can cause functional disorders of various organs and systems.

The macro-level model includes three submodels. The stream submodel describes how functional disorders develop in organs and systems in the human body; the kinetic submodel focuses on how chemicals are introduced, excreted, metabolized or deposited in the body; the neural-humoral submodel describes regulatory mechanisms. In its turn, each submodel of the macro-level model includes several interrelated meso-level models; we are going to describe them in greater detail in our future works.

3. MATHEMATICAL STATEMENT

3.1. The stream submodel. Changes in damage of organs and systems in the human body occur due to effects of several mechanisms. The most significant ones include natural ageing, organ self-recovery, accumulation of damage due to harmful environmental exposures beyond their safe levels (divided into two components), and recovery of functions due to treatment. The rate of changes $d_j(t)$ in damage $D_j(t)$ of the *j*-th organ (system) is assumed to be determined by a sum of damage velocities $d_{kj}(t)$ as per the following mechanisms:

$$\frac{dD_j(t)}{dt} \equiv d_j(t) = \sum_{k=1}^{5} d_{kj}(t),\ j = \overline{1,\ J}\ .$$

It is noteworthy that an assumption about additivity of damage velocities does not lead to the model becoming linear since there are complex non-linear relationships between all the parameters included into the submodels of the macro-level model.

At a first approximation, natural ageing can be described by the following relationship:

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$$d_{1j}(t) = \alpha_j^0 + \alpha_j^1 D_j(t), \quad (1)$$

where $\alpha_j^0 > 0$ and $\alpha_j^1 > 0$ are coefficients that describe rate of ageing for the *j*-th organ, [1/s]. The relationship (1) includes the summands embodying two different ageing mechanisms. The first summand describes how damage is growing over the whole lifetime. Generally, it is a non-decreasing function of time. To make things simple at a first approximation, we consider α_j^0 a constant. The second summand in the relationship (1) makes an additional contribution to damage due to more intense functioning of an undamaged part of an organ in case there are some structural disorders. This healthy part of an organ naturally has to operate in a forced regime so that all the vital processes are performed properly. This forced operation reduces cell life and leads to accelerated destruction of an organ. Therefore, this summand is to depend on damage of an organ $D_j(t)$ and on the coefficient α_j^1, which describes influence of organ deterioration on damage rate.

Organ self-recovery (reparation) is related to functionality and can be given as:

$$d_{2j}(t) = -\beta_j (1 - D_j(t))^{n_j}, \quad (2)$$

where $\beta_j > 0$ is a coefficient that describes the recovery rate for the damage of *j*-th organ, [1/s]. Any organ recovers naturally during the whole lifetime and this recovery is an uninterrupted process (cell division and differentiation); the recovery function weakens over time due to defects accumulating in cells. Generally, the coefficient β_j is also a time function; we assume this parameter to be constant at this stage in the model development.

All the interactions between organs and the environment are performed by streams of substances and energy. Stream is an amount of a substance or energy that is entered into an organ per a time unit and has some effects on damage developing in this organ.

The value $p_{ji}(t)$ reflects the *i*-th stream into the *j*–th organ, [kg/s]; the inflow into an organ is assumed to be positive and the outflow from it is assumed to be negative. For each organ, we consider both streams coming directly from the environment and through other organs and systems as well (for example, oxygen is delivered to the circulatory system through the respiratory system). In the latter case, when identifying a stream, it is necessary to consider functionality of an organ that receives it from the environment. The value $p_{ji}^N(t)$ reflects the *i*-th stream into the *j*-th organ under normal conditions (the value of a normal stream depends on age and how the body functions at a current moment; for example, normal values under physical loads can be quite different from those in rest). If we consider a stream of substances (or energy), for which the normal value is equal to zero, our reference value would be the maximum permissible stream, which does not cause irreversible changes in an organ over physically infinite (that is, an individual's lifetime) duration of exposure. Streams describe chemical and physical (noise, electromagnetic radiation, and vibration) factors.

An equation that relates a stream and a level in blood can be written for any substance penetrating an organ from blood:

$$p_{ji}(t) = \gamma_{ji} C_i^b(t), \quad (3)$$

where $C_i^b(t)$ is a level of *i*-th chemical in blood, [kg/m^3]; $\gamma_{ji} \geq 0$ is a coefficient of proportionality that describes how fast the *i*-th chemical is entered from blood into the *j*-th organ, [m^3/s]. For energy streams, the relationship (3) and dimensionality of values depend on a type of an affecting factor.

We need a special function $\langle x \rangle$, so called McCauley brackets, to describe effects produced by environmental factors: $\langle x \rangle = \max(0,\ x)$.

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Damage caused by environmental exposures can occur due to insufficient entry of benign streams or excessive entry of harmful ones. These different mechanisms of damage accumulation should be described with separate relationships. Considering all the introduced denominations, negative effects of harmful streams beyond their safe limits (chemicals, noise, electromagnetic irradiation, etc.) can be described by:

$$d_{3j}(t) = \sum_i \chi_{ji}^0 \left\langle \frac{p_{ji}(t)}{p_{ji}^N(t)} - 1 \right\rangle, \tag{4}$$

where $d_{3j}(t)$ is the rate of change in damage of the *j*-th organ due to exposure to a harmful stream beyond its safe limit; $p_{ji}^N(t)$ is the standard (maximum permissible) *i*-th stream into the *j*-th organ; $\chi_{ji}^0 \geq 0$ is a coefficient that describes influence of negative factors on damage of an organ, [1/s]. The relationships (4) describe how fast damage of an organ changes in case an exposure is beyond its safe limits.

Effects produced by insufficient entry of benign streams (nutrients, vitamins, microelements, etc.) into the human body can be given by:

$$d_{4j}(t) = \sum_i \chi_{ji}^1 \left\langle 1 - \frac{p_{ji}(t)}{p_{ji}^P(t)} \right\rangle, \tag{5}$$

where $d_{4j}(t)$ is the rate of change in damage of the *j*-th organ due to insufficient entry of benign streams; $p_{ji}^P(t)$ is the standard *i*-th (benign) stream into the *j*-th organ; $\chi_{ji}^1 \geq 0$ is a coefficient describing influence of benign streams and factors on damage of an organ, [1/s]. When the model is complicated further, linear right parts in the relationships (4)–(5) (sectionally) can be replaced with non-linear ones (for example, power law).

A relationship that describes treatment effects can be written as:

$$d_{5j}(t) = \sum_i \chi_{ji}^2 H\left(\frac{p_{ij}(t)}{p_{ji}^{L\min}(t)} - 1 \right) \left\{ \left(\frac{p_{ji}(t) - p_{ji}^{L\min}(t)}{p_{ji}^{L\max}(t) - p_{ji}^{L\min}(t)} \right) \left(\frac{p_{ji}(t) - p_{ji}^{L\min}(t)}{p_{ji}^{L\max}(t) - p_{ji}^{L\min}(t)} - 1 \right) \right\}^q, \tag{6}$$

where $d_{5j}(t)$ is the rate of change in damage of the *j*-th organ due to effects of healing streams; $p_{ji}^{L\min}(t)$ is the minimal stream of the *i*-th treatment factor into the *j*-th organ able to produce a healing effect; $p_{ji}(t) \in \left(p_{ji}^{L\min}(t); p_{ji}^{L\max}(t) \right)$. The right part of (6) is negative, which corresponds to a decrease in damage of an organ (treatment); $p_{ji}^{L\max}(t)$ is the maximum stream of the *i*-th treatment factor into the *j*-th organ and any stream beyond this value makes $d_{5j}(t)$ change its sign (treatment factor overdose); $\chi_{ji}^2 \geq 0$ is the coefficient describing influence of treatment factors on damage of an organ, [1/s]. The Heaviside step function is given by $H(x)$ ($H(x) = 1$ at $x > 0$ and $H(x) = 0$ at $x \leq 0$), $q \geq 1$ is an odd natural exponent. $d_{5j}(t)$ Reaches its minimum value (the maximum healing effect) at $p_{ij}(t) = (p_{ji}^{L\max}(t) + p_{ji}^{L\min}(t))/2$.

Generally, all the material (physiological) indicators included in the equations are functions (or, possibly, functionals of past history) of organ conditions.

Given all the introduced concepts and denominations and accepting a hypothesis that rates of damage due to different factors are additive, we can present the following structure of equations to describe how damage develops in organs and systems of the human body:

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$$\frac{dD_j(t)}{dt} = \alpha_j^0 + \alpha_j^1 D_j(t) - \beta_j \left(1 - D_j(t)\right)^{n_j} + \sum_i \chi_{ji}^0 \left\langle \frac{p_{ji}(t)}{p_{ji}^N(t)} - 1 \right\rangle + \sum_i \chi_{ji}^1 \left\langle 1 - \frac{p_{ji}(t)}{p_{ji}^P(t)} \right\rangle +$$

$$+ \sum_i \chi_{ji}^2 H\left(\frac{p_{ij}(t)}{p_{ji}^{L\min}(t)} - 1 \right) \left\{ \left(\frac{p_{ji}(t) - p_{ji}^{L\min}(t)}{p_{ji}^{L\max}(t) - p_{ji}^{L\min}(t)} \right) \left(\frac{p_{ji}(t) - p_{ji}^{L\min}(t)}{p_{ji}^{L\max}(t) - p_{ji}^{L\min}(t)} - 1 \right) \right\}^q, \qquad (7)$$

$$D_j(t) \in [0,1],\ j = \overline{1,\ J}.$$

This structure of equations shows a general overview of damage development and considers self-destruction (natural ageing), self-recovery (reparation), accumulation of damage due to streams of chemicals beyond their safe levels, and functional recovery due to treatment. The systems in the body are interrelated through the streams $p_{ji}(t)$. Intensity of these streams depends on damage of organs, entry, excretion, metabolism, etc.

To complete the system of equations (7), it is necessary to add initial conditions, that is, to identify functional disorders at the initial moment of time. To do that, we suggest solving a diagnostic task. Damage indicators are identified for most basic system by performing clinical and laboratory tests, ultrasound, functional and other specialized examinations [25–28]. Selection of functional markers x_i is the initial stage in solving this diagnostic task aimed at identifying functional disorders in a given organ or a system of organs. It is necessary to identify to what extent each marker describes the functional state of a given system. To do that, we introduce a concept of functional disorders as per the *i*-th marker Φ_i, where $\Phi_i \in [0,1], \Phi_i = 0$ if a value of a marker is within its physiological range; $\Phi_i = 1$ if a marker reaches its extreme possible values that describe a condition close to total loss of functions. If marker values are somewhere between the boundary of the physiological range and the extreme possible value, the Φ_i value changes between 0 and 1 according to the present (for example, linear) law. In case a qualitative marker is used, the Φ_i value is identified by expert evaluation. Damage of an organ or a system is identified by the weighted sum of functional disorders: $D = \sum_i a_i \Phi_i$, where the coefficients a_i are determined by experts. Therefore, damages of organs and systems $D_j(t_0)$ obtained by solving the diagnostic tasks at an age of t_0 can be used as initial conditions for the system (7).

The relationships (7) are a system of ordinary differential equations, generally, with a non-linear right part [29]. If streams are constant, the system (7) has only one analytical solution since the right part (7) in this is continuously differentiable in the whole domain. If streams are defined by discrete functions or derivatives of these functions have discontinuity, then the conditions of the Cauchy's theorem that the problem has a (unique) analytic solution are not met. The graphs showing the solution to the system are a family of exponential curves depending on values of the coefficients and initial conditions.

Generally, substance streams depend on damage of various organs and the stationary solution to the system (7) can be unstable. Figure 1 provides an example, a phase portrait depicting damage of two organs (the kidneys, $D_1(t)$; the lungs, $D_2(t)$). The kidneys are affected by one harmful substance with its levels changing over time according to the kinetic model, which is described in detail below. The resulting phase trajectories are curves coming from any point in the square $[0,1] \times [0,1]$ area depending on the initial conditions. The curves are directed at one of the square sides. The equilibrium point is an unstable node.

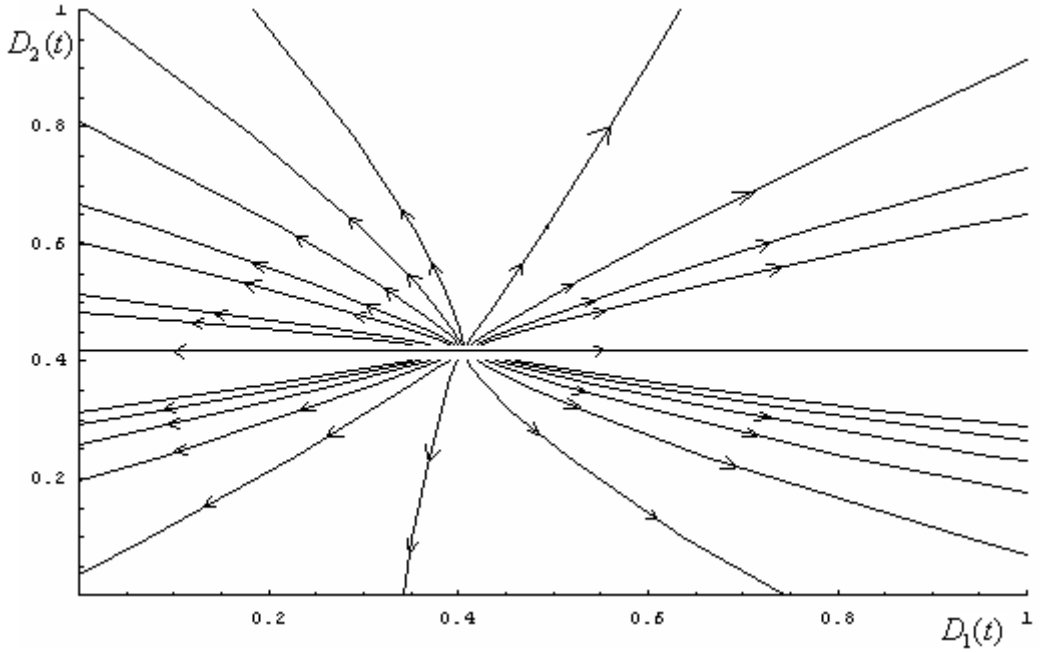

Fig. 1. Phase portrait depicting damage of two organs.

The equation (7) includes chemical levels in blood (the relationship ratio (3)). It is necessary to use models of toxicokinetic processes to compute these levels.

3.2. The kinetic model. The mathematical kinetic model is based on physiological models. The structural basis of a physiological model is a section in the body where a chemical concentration is homogeneous. This section can be a specific functional or anatomic part of an organ. Physiological models have some advantages. They are able to describe how chemicals are distributed in any actual organ and tissue; they give an opportunity to establish how physiological parameters influence chemical levels in tissues; they provide an easy way to describe complex dosage regimens and saturation in metabolism and complex formation. Kinetic constants are obtained empirically in physiological models when actual biological or chemical processes are investigated. Obtained kinetic parameters can be extrapolated on other external conditions and physiological states [30–32]; in such cases it is necessary to verify results of extrapolation by thorough empirical examinations.

Changes in chemical concentrations in the body occur due to several mechanisms. They involve transporting through some biological membranes and include entry from the environment, accumulation, metabolism and excretion. Membrane systems of the body have similar structures but different functional properties. They are mobile structures created by protein-phospholipid complexes and have limited permeability for different chemicals. A mechanism for chemicals passing through membranes is rather complicated since it is influenced not only by functional peculiarities of membranes themselves but also certain functions of protoplasm and cellular proteins. Substance kinetics in the body includes three ways of entry: oral, inhalation, and subcutaneous (through skin). It is noteworthy that chemicals can also be excreted through these ways.

The equation to describe absorption and excretion of harmful chemicals by the lungs, skin and gastrointestinal tract, was based on the Fick equation:

$$V_{ji}^{A-E}(t) = \lambda_{ji}^{A-E} F_j(t)(\bar{C}_i^j(t) - h_{ji}^{A-E} C_i^b(t)), \tag{8}$$

where $V_{ji}^{A-E}(t)$ is the rate of changes in the level of *i*-th chemical in blood due to the *j*-th ($j = \overline{1,\mathrm{J}}$) absorption-excretion organ, [kg/(m^3·s)] (as agreed, the rate of changes in levels of a chemical is positive for an inflow and negative for an outflow). $\lambda_{ji}^{A-E} \geq 0$ Is the constant of

the entry (excretion) rate for the *i*-th chemical through the *j*-th organ responsible for entry (excretion), [1/s]; h_{ji}^{A-E} is the dimensionless coefficient as per the *i*-th chemical to describe equilibrium between blood and ambient air; $\bar{C}_i^j(t)$ is the level of the *i*-th chemical in the *j*-th medium (in inhaled air or digestive mix depending on an entry path), [kg/m^3]; $F_j(t)$ is the functionality of the *j*-th organ responsible for entry (excretion).

If we rely on principles for creating compartment physiological models, we can write the following equation to describe how chemicals are excreted by the kidneys and liver:

$$V_{ji}^E(t) = -\lambda_{ji}^E F_j(t) C_i^b(t), \tag{9}$$

where $V_{ji}^E(t)$ is the rate of changes in the level of the *i*-th chemical in blood due to the *j*-th organ responsible for excretion, [kg/(m^3·s)]; $\lambda_{ji}^E \geq 0$ is the rate constant of the *i*-th chemical excretion through the *j*-th excretion organ, [1/s]; $F_j(t)$ is the functionality of the *j*-th organ responsible for excretion.

The Michaelis–Menten equation, the main one of enzyme kinetics, is applied to describe chemical metabolism with enzymes [33–36]. The considered relationship describes dependence of an enzyme-catalyzed reaction rate on a substrate and enzyme level:

$$V_{ik}^M(t) = \frac{\lambda_{ik}^{cat} \cdot \sum_j (F_j(t) E_{ikj}^N(t)) \cdot C_i^b(t)}{K^{ik} + C_i^b(t)}, \tag{10}$$

where $V_{ik}^M(t)$ is the rate of changes in the level of the *i*-th chemical in blood within formation of the *k*-th chemical due to an enzyme [kg/(m^3·s)] (the number of chemicals can change in different variants of the model use); $\lambda_{ik}^{cat} \geq 0$ is the coefficient that describes the rate of metabolism, [s^{-1}]; $E_{ikj}^N(t)$ is the standard level of an enzyme produced by the *j*-th organ that transforms the *i*-th chemical into the *k*-th one, [kg/m^3]; $F_j(t)$ is the functionality of the *j*-th organ producing an enzyme; K^{ik} is the Michaelis constant that describes the affinity between an enzyme and substrate [kg/m^3]. At this stage, a reaction with only one enzyme is described; in case a reaction requires several enzymes or a reaction has several stages, the equation (10) becomes more complicated. For example, the Michaelis constant for a multi-stage reaction is computed considering rate constants identified for each stage.

Chemicals stream from organs where they are deposited by diffusion provided there is a gradient of concentrations between an organ and blood:

$$V_{ji}^{Sb}(t) = \lambda_{ji}^S F_j(t)(C_i^j(t) - h_{ji}^S C_i^b(t)), \tag{11}$$

where $V_{ji}^{Sb}(t)$ is the rate of changes in the concentration of the *i*-th chemical in blood due to entry form the *j*-th organ, [kg/(m^3·s)]; $\lambda_{ji}^S \geq 0$ is the rate constant for the entry of the *i*-th chemical from the *j*-th organ in blood, [1/s]; h_{ji}^S is the dimensionless coefficient of equilibrium between blood and a depositing organ as per the *i*-th chemical; $C_i^j(t)$ is the concentration of the *i*-th chemical in the *j*-th organ, [kg/m^3]; $F_j(t)$ is the functionality of the *j*-th depositing organ.

The rate of changes in the concentration $V_{ji}^{Sd}(t)$ of the *i*-th chemical in the *j*-th organ due to entry from blood is determined considering the formula (11):

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$$V_{ji}^{Sd}(t) = -\frac{U^b}{U_j^d} V_{ji}^{Sb}(t), \tag{12}$$

where U^b, U_j^d is a volume of blood and biological medium of a depositing organ accordingly.

Based on balance equations (conservation of mass), a change in the concentration of the *i*-th chemical in blood and organs where it accumulates can be written as:

$$\begin{cases} \dfrac{dC_i^b(t)}{dt} = \sum\limits_j V_{ji}^{A\text{-}E}(t) + \sum\limits_j V_{ji}^{E}(t) + \sum\limits_j V_{ji}^{Sb}(t) - \sum\limits_k V_{ik}^{M}(t) + \sum\limits_k V_{ki}^{M}(t), \\ \dfrac{dC_i^j(t)}{dt} = V_{ji}^{Sd}(t). \end{cases}, \tag{13}$$

The coefficients in the equations (8–11) generally depend on physical properties of organs such as sizes, mass, and stream capacity of their membranes. To solve the system, it is necessary to set initial conditions as regards chemical levels in blood and organs where they accumulate. The relationships (13) are connected with the stream model through chemical levels in blood and functionality of organs and systems.

We would like to consider a more special case of the equation (13) for one chemical entered with inhaled air without any metabolism and investigate whether it is stable and has a solution. We assume the chemical level in ambient air to be constant and damage of the relevant systems to equal 0; in this case, the relationship (13) reduces to the system of linear differential equations:

$$\begin{cases} \dfrac{dC_1(t)}{dt} = \lambda^{A-E}(\bar{C} - h^{A-E}C_1(t)) - \lambda^{E}C_1(t) + \lambda^{S}(C_2(t) - h^{S}C_1(t)), \\ \dfrac{dC_2(t)}{dt} = -\lambda^{S}(C_2(t) - h^{S}C_1(t)), \\ C_1(0) = C_1^0, \\ C_2(0) = C_2^0, \end{cases}, \tag{14}$$

where $C_1(t)$, $C_2(t)$, $\bar{C}$ are the chemical levels in blood, an organ where it accumulates, and ambient air accordingly; λ^{A-E}, λ^{E}, λ^{S} are the coefficients to describe exchange between the lungs and blood, the kidneys and the environment, an organ of accumulation and blood accordingly; h^{A-E}, h^{S} are the solubility coefficients.

The system has the unique analytical solution since its right part is continuous and continuously differentiable. The point

$$\left(\frac{\lambda^{A-E}\bar{C}}{\lambda^{A-E}h^{A-E} + \lambda^{E}}; \frac{h^{S}\lambda^{A-E}\bar{C}}{\lambda^{A-E}h^{A-E} + \lambda^{E}} \right)$$

is the one where the system is in equilibrium. It is at this point that the right parts in the equations (14) turn to zero [37].

Identification of a solution type and stability of equilibrium for the system of linear differential equations (14) reduces to identifying eigenvalues of the matrix of the analyzed system:

$$\begin{pmatrix} -(\lambda^{A-E}h^{A-E} + \lambda^{s}h^{s} + \lambda^{E}) & \lambda^{s} \\ \lambda^{s}h^{s} & -\lambda^{s} \end{pmatrix}. \tag{15}$$

The eigenvalues of the matrix (15) k_1, k_2 can be identified by equating the determinant to zero:

$$\begin{vmatrix} -(\lambda^{A-E}h^{A-E} + \lambda^s h^s + \lambda^E) - k & \lambda^s \\ \lambda^s h^s & -\lambda^s - k \end{vmatrix} = 0 \qquad (16)$$

By transforming (16), we can get a quadratic equation; its roots determine a solution type and the stability of the whole system (14):

$$k^2 + k(\lambda^{A-E}h^{A-E} + \lambda^S h^S + \lambda^E + \lambda^S) + \lambda^S(\lambda^{A-E}h^{A-E} + \lambda^E) = 0 \qquad (17)$$

The equation (17) has two real negative roots since the coefficients in the (17) are positive, and the discriminant of the characteristic equation is non-negative:

$$(\lambda^{A-E}h^{A-E} + \lambda^S h^S + \lambda^E + \lambda^S)^2 - 4\lambda^S(\lambda^{A-E}h^{A-E} + \lambda^E) \geq 0, \qquad (18)$$

therefore, the equilibrium position is a stable node.

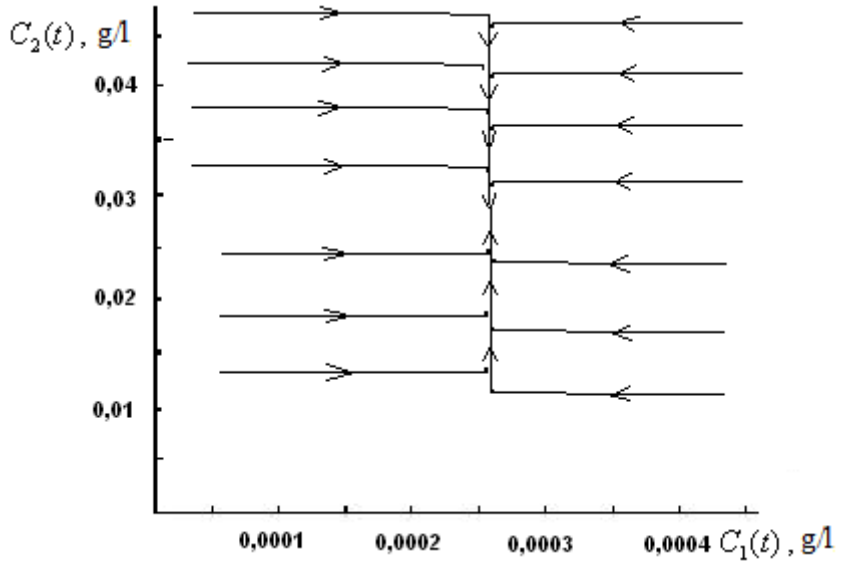

Fig. 2. The phase portrait of the 'level in blood – level in depot' system.

Figure 2 shows the phase portrait for the system (14) (the coefficients correspond to the kinetic parameters describing how lead is distributed in the human body, the procedure for identifying these coefficients is described below; the equilibrium point is (0.000267 g/l, 0.0281 g/l); $\lambda^{A-E} = 0.21$ [1/s]; $\lambda^E = 2.19 \cdot 10^{-7}$ [1/s]; $\lambda^S = 4.05 \cdot 10^{-10}$ [1/s]; $h^S = 105.2$; $h^{A-E} = 5.55 \cdot 10^{-5}$; $\bar{C} = 15$ μg/m^3). If chemical levels are constant in the environment, their concentrations in blood reach a stationary level. Any deviation from this stationary level can occur due to disrupted excretion and entry of chemicals. The rate of chemical exchange between ambient air and blood is significantly higher than the rate of chemical entry into organs where it is deposited. If a chemical level in ambient air is constant, blood can be saturated with this toxicant over several minutes or hours but deep depositing of it, for example, in bone tissues can take many years. If a chemical is entered in low doses, equilibrium between blood and a depot-organ can be unreachable within a usual human lifespan.

3.3. The neuro-humoral model. Homeostasis is provided in the human body by proper immune system functioning. This system is a unique self-regulating structure consisting of various populations and sub-populations of lymphoid cells, organs (the bone marrow) and cells (T-helpers, macrophages) that constantly interact with each other. However, their vital

activity, activation, proliferation (growth), and differentiation largely depend on other systems in the body, primary, the endocrine and nervous system. The immune, endocrine, and nervous system interact with each other all the time thereby performing mutual control of their functions. Their integration with functions performed by other organs and systems provides life of the human body as a single whole [38–40].

Changes in hormone levels in the body are caused by the nervous and endocrine system functioning. The immune, endocrine, and nervous system are interrelated in their functioning and create functional feedback-like effects. Immune-competent cells are able to synthesize some hormones and neuropeptides as well as cytokines that produce regulatory effects on the nervous and endocrine systems [41, 42].

The equation for hormone levels in blood can be written as:

$$g^r(t) = \sum_k F_k(t)\left(g_{rk}^N(t) + \lambda_{rk} \sum_j \left\langle \frac{C_j^b(t)}{C_j^{bN}(t)} - 1 \right\rangle \right), \tag{19}$$

where $g^r(t)$ is the level of the *r*-th hormone in blood, [kg/m^3]; $F_k(t)$ is the functionality of the *k*-th organ that releases this hormone; $g_{rk}^N(t)$ is the level of the *r*-th hormone in blood that corresponds to proper functioning of the *k*-th organ, [kg/m^3]; λ_{rk} is the coefficient describing influence of factors on additional release of the analyzed hormone, can be either negative or positive depending on the action mechanisms of the hormone, [kg/m^3]; $C_j^{bN}(t)$ is the reference level of the *j*-th chemical in blood, [kg/m^3].

The equation (13) can be re-written considering effects produced by hormones on levels of harmful chemical in blood as follows:

$$\begin{cases} \dfrac{dC_i^b(t)}{dt} = \sum\limits_j V_{ji}^{A\text{-}E}(t) \cdot \left(1 + \phi_{ji}^r \cdot g_{ji}^r(t)\right) + \sum\limits_j V_{ji}^E(t) \cdot \left(1 + \phi_{ji}^r \cdot g_{ji}^r(t)\right) + \\ \qquad + \sum\limits_j V_{ji}^{Sb}(t) \cdot \left(1 + \phi_{ji}^r \cdot g_{ji}^r(t)\right) - \sum\limits_k V_{ik}^M(t) + \sum\limits_k V_{ki}^M(t), \\ \dfrac{dC_i^j(t)}{dt} = V_{ji}^{Sd}(t) \cdot \left(1 + \phi_{ji}^r \cdot g_{ji}^r(t)\right), \end{cases} \tag{20}$$

where ϕ_{ji}^r is the coefficient describing effects of the *r*-th hormone on changes in levels of the *i*-th chemical through the *j*-th entry (or excretion, or accumulation) way (organ). If $\phi_{ji}^r > 0$, then the hormone enhances effects produced by a factor, $\phi_{ji}^r < 0$ means it weakens them.

The system of equations (19), (20) is written for the general case; specific neuro-humoral chains require additional research.

If we combine the relationships (7)–(13), (19), (20), we can write the whole system of equations within the mathematical model for describing evolution of functional disorders:

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$$
\begin{cases}
\dfrac{dD_j(t)}{dt} = \alpha_j^0 + \alpha_j^1 D_j(t) - \beta_j \left(1 - D_j(t)\right)^{n_j} + \sum\limits_i \chi_{ji}^0 \left\langle \dfrac{p_{ji}(t)}{p_{ji}^N(t)} - 1 \right\rangle + \sum\limits_i \chi_{ji}^1 \left\langle 1 - \dfrac{p_{ji}(t)}{p_{ji}^P(t)} \right\rangle + \\
+ \sum\limits_i \chi_{ji}^2 H\left(\dfrac{p_{ij}(t)}{p_{ji}^{L\min}(t)} - 1 \right) \left\{ \left(\dfrac{p_{ji}(t) - p_{ji}^{L\min}(t)}{p_{ji}^{L\max}(t) - p_{ji}^{L\min}(t)} \right) \left(\dfrac{p_{ji}(t) - p_{ji}^{L\min}(t)}{p_{ji}^{L\max}(t) - p_{ji}^{L\min}(t)} - 1 \right) \right\}^q, D_j(t) \in [0,1] \\
F_j(t) = \left(1 - D_j(t)\right)^{n_j}, n_j \geq 1; \\
p_{ji}(t) = \gamma_{ji} C_i^b(t); \\
g^r(t) = \sum\limits_k F_k(t) \left(g_{rk}^N(t) + \lambda_{rk} \sum\limits_j \left\langle \dfrac{C_j^b(t)}{C_j^{bN}(t)} - 1 \right\rangle \right); \\
\dfrac{dC_i^b(t)}{dt} = \sum\limits_j \lambda_{ji}^{A-E} F_j(t) (\bar{C}_i^j(t) - h_{ji}^{A-E} C_i^b(t)) \cdot \left(1 + \phi_{ji}^r \cdot g_{ji}^r(t)\right) - \\
- \sum\limits_j \lambda_{ji}^E F_j(t) C_i^b(t) \cdot \left(1 + \phi_{ji}^r \cdot g_{ji}^r(t)\right) + \sum\limits_j \lambda_{ji}^S F_j(t) (C_i^j(t) - h_{ji}^S C_i^b(t)) \cdot \left(1 + \phi_{ji}^r \cdot g_{ji}^r(t)\right) - \\
- \sum\limits_k \dfrac{\lambda_{ik}^{cat} \cdot \sum\limits_j (F_j(t) E_{ikj}^N(t)) \cdot C_i^b(t)}{K^{ik} + C_i^b(t)} + \sum\limits_k \dfrac{\lambda_{ki}^{cat} \cdot \sum\limits_j (F_j(t) E_{ikj}^N(t)) \cdot C_k^b(t)}{K^{ki} + C_k^b(t)}; \\
\dfrac{dC_i^j(t)}{dt} = -\dfrac{U^b}{U_j^d} \lambda_{ji}^S F_j(t) (C_i^j(t) - h_i C_i^b(t)).
\end{cases}
\tag{21}
$$

The system of equations (21) combines the stream, kinetic, and neuro-humoral submodels. The common method for identifying the model coefficients relying on available experimental data involves finding a solution to the optimization task. This solution means identifying parameters of a target function that provide minimal deviation of results obtained by numeric modeling from experimental data. Parameters should be identified for the whole system of equations; to do that, it is necessary to perform periodical monitoring of organs and systems during the whole lifetime; this monitoring should include clinical and laboratory tests as well as functional examinations with measuring contamination levels in biological media. Besides, it is necessary to know levels of exposure to analyzed factors. In actual conditions, periodical monitoring can be replaced with creating samples that are made of ‘similar’ individuals form different age groups (they should be close as per physiological parameters and have similar exposures in their history). In case experimental data are incomplete, it is necessary to use literature sources, for example, data on additional incidence caused by specific exposure or data on kinetics of a chemical in the human body.

At this stage in modeling, we have obtained some qualitative results for different scenarios to demonstrate how the macro-level model operates. We identified complex parameters describing natural accumulation of functional disorders in the human body for major organs and systems at a first approximation. Identification relied on using statistical data on incidence and mortality among adult population in the Perm region over 2009–2011. Expert evaluations were applied to rank each diseases as per its severity, the score varied between 0 (mild diseases) and 1 (fatal diseases and deaths). A parameter can be identified for each age group; it corresponds to regional functional disorders of organs and systems and is identified based on the ratio of a sum of diseases cases considering their severity and deaths and population numbers. The 5th percentile of damage as per different areas in each age group in 2009–2011 was used to identify coefficients for the equation describing evolution of functional disorders without any exposures. Damage in an age group of 20–24 years was

applied as initial data D (22 years). Table 1 provides the identification results (the exponent in the recovery summand is $n = 1$).

Table 1. The model parameters

System	$\alpha_j^0 - \beta_j$	$\alpha_j^1 + \beta_j$	$D(22)$
Musculoskeletal system	0.00126±0.000335*	0.0292±0.0074*	0.0187
Respiratory system	–0.000807±0.000391	0.0728±0.0138*	0.0151
Digestive system	–0.000626±0.000476	0.0354±0.0113*	0.0326
Cardiovascular system	0.002394±0.000683*	0.0453±0.0077*	0.0079
Hearing organs	–0.000083±0.00005	0.0484±0.0149*	0.0024
Endocrine system	–0.000131±0.000077	0.0748±0.0126*	0.0032
Visual organs	–0.000584±0.000226*	0.0747±0.0135*	0.0103
Central nervous system	–0.000232±0.000197	0.0589±0.0384	0.0044
Genitourinary system	–0.00073±0.000367	0.0692±0.0315	0.0108

* means the level of significance is $p < 0.05$

Parameters of exposure factors were identified separately for each factor as per data available in literature. Thus, a relationship is identified between lung cancer cases and a number of cigarettes smoked a day [43]. Considering additional lung cancer cases associated with smoking, regional levels of functional disorders were computed for each age group. These data made it possible to identify the parameter that described effects of smoking: $\chi^0 = (9.7 \pm 3.1) \cdot 10^{-5}$ [1/s]. A standard condition for the smoking factor is one cigarette a day. The parameters of the kinetic model showing how lead is distributed in the human body, similar to the (14) are available in literature [44]; accordingly, we took the following coefficients: $\lambda^E = 2.19 \cdot 10^{-7}$ [1/s], $\lambda^S = 4.05 \cdot 10^{-10}$ [1/s], $h^S = 105.2$. Since an increase in airborne lead levels by 0.001 μg/l increases lead level in blood by 18 μg/l [45], h^{A-E} is taken as equal to $5.55 \cdot 10^{-5}$; if a new stationary level is achieved within 24 hours, then $\lambda^{A-E} = 0.21$ [1/s]. A lead level in blood that does not produce any negative effects on the kidneys [46] is taken as equal to 10^{-4} kg/m^3. A parameter describing effects of lead on the kidneys was identified by expert evaluations $\chi^0 = 5 \cdot 10^{-5}$ [1/year].

4. NUMERIC IMPLEMENTATION OF THE MODEL: AN EXAMPLE

To solve the system of equations (21), we used a developed software module. It gives an opportunity to compute values of parameters that describe damage of specific systems in the body depending on intensity of exposure factors. The numeric solution of the system of equations was accomplished using finite-difference schemes; to approximate the first derivatives in time, the right finite differences were used. Table 2 provides values of exposure factors for several possible scenarios.

The analyzed scenarios consider three systems: the lungs ($j = 1$), the kidneys ($j = 2$), and the musculoskeletal system ($j = 3$). The musculoskeletal system is a depot organ for lead with damage independent of time and taken as equal to zero $D_3(t) = 0$ for all the scenarios. The scenario 1 covers only natural ageing and recovery (the parameter in the recovery member is $n = 1$) of both organs. In the remaining scenarios, a contribution to damage is made (in addition to natural ageing) by a toxicant (lead $i = 1$), changes of its levels in the body being identified as per the suggested kinetic model (14). Airborne lead levels are constant and given as $\bar{C} = 15 \cdot 10^{-9}$ kg/m^3 over the whole lifetime, which corresponds to living close to an industrial enterprise emitting lead in ambient air. In all the analyzed scenarios, the initial lead

level in blood and a depositing organ is equal to zero at birth (t = 0 years). In the scenario 3, kidney diseases are treated periodically; in the scenario 4, constant negative effects on the lungs (i = 2) are added starting from a certain moment of time (in reality, such a scenario may correspond to smoking). For the smoking factor, we assume that $p_{12}(t) / p_{12}^N(t) = S(t) / S^N(t)$, where $S(t)$ is the number of cigarettes smoked a day (in the scenario 4, $S(t)$=20 cigarettes/day after 30 years; prior to this moment, $S(t)$=0), $S^N(t)$ is the number of cigarettes smoked a day that does not have any negative effects (is taken as 1 cigarette smoked a day).

Table 2. Exposure factors for various scenarios

Scenario	Organ	Chemical (lead), inhalation exposure	Lifestyle factor (smoking)	Treatment
1	kidneys	–	–	–
	lungs	–	–	–
2	kidneys	$\bar{C}$=15 μg/m^3	–	–
	lungs	–	–	–
3	kidneys	$\bar{C}$=15 μg/m^3	–	Recovery of D by 0.001 over a year after 40 years
	lungs	–	–	–
4	kidneys	$\bar{C}$=15 μg/m^3	–	–
	lungs	–	20 cigarettes a day after 30 years	–

The system (21) is written as:

$$\begin{cases} \dfrac{dD_1(t)}{dt} = \alpha_1^0 + \alpha_1^1 D_1(t) - \beta_1\left(1 - D_1(t)\right) + \chi_{12}^0 \left\langle \dfrac{p_{12}(t)}{p_{12}^N(t)} - 1 \right\rangle, D_1(t) \in [0,1]; \\ \dfrac{dD_2(t)}{dt} = \alpha_2^0 + \alpha_2^1 D_2(t) - \beta_2\left(1 - D_2(t)\right) + \chi_{21}^0 \left\langle \dfrac{p_{21}(t)}{p_{21}^N(t)} - 1 \right\rangle, D_2(t) \in [0,1]; \\ F_1(t) = 1 - D_1(t); \\ F_2(t) = 1 - D_2(t); \\ p_{21}(t) = \gamma_{21} C_1^b(t); \\ \dfrac{p_{12}(t)}{p_{12}^N(t)} = \dfrac{S(t)}{S^N(t)} \\ \dfrac{dC_1^b(t)}{dt} = \lambda_{11}^{A-E} F_1(t)(\bar{C}_1^1(t) - h_{11}^{A-E} C_1^b(t)) - \lambda_{21}^E F_2(t) C_1^b(t) + \lambda_{31}^S (C_1^3(t) - h_{31}^S C_1^b(t)) \\ \dfrac{dC_1^3(t)}{dt} = -\lambda_{31}^S (C_1^3(t) - h_{31}^S C_1^b(t)). \end{cases} \quad (22)$$

Treatment is not obviously considered in the system (22); in the scenario (3), effects of treatment are simplified: $D_2(t)$ decreases by 0.001 times once a year after 40 years. Considering the relationship $p_{21}(t) = \gamma_{21} C_1^b(t)$, we can write $p_{21}^N(t) = \gamma_{21} C_1^{bN}(t)$, where $C_1^{bN}(t)$, a lead level in blood that has no negative effects on the kidneys, is taken as equal to 10^{-4} kg/m^3. In this case, the parameter γ_{21} can be excluded: ($\dfrac{p_{21}(t)}{p_{21}^N(t)} = \dfrac{\gamma_{21} C_1^b(t)}{\gamma_{21} C_1^{bN}(t)} = \dfrac{C_1^b(t)}{C_1^{bN}(t)}$). The parameters λ_{11}^{A-E}, h_{11}^{A-E}, λ_{21}^E, λ_{31}^S, h_{31}^S correspond to those in the system (14) (without

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indexes). The coefficients $\chi_{12}^0 = (9.7 \pm 3.1) \cdot 10^{-5}$ [1/year], $\chi_{21}^0 = 5 \cdot 10^{-5}$ [1/year] correspond to effects of smoking on the lungs and lead on the kidneys. We consider only inhalation way of entry for lead and the chemical level in ambient air is constant $\bar{C}_1^1 = 15 \cdot 10^{-9}$ kg/m^3.

We would like to analyze the graph showing how damage develops in two organs participating in distribution of harmful chemical flows in blood, the lungs and the kidneys, within the suggested scenarios (Figure 3).

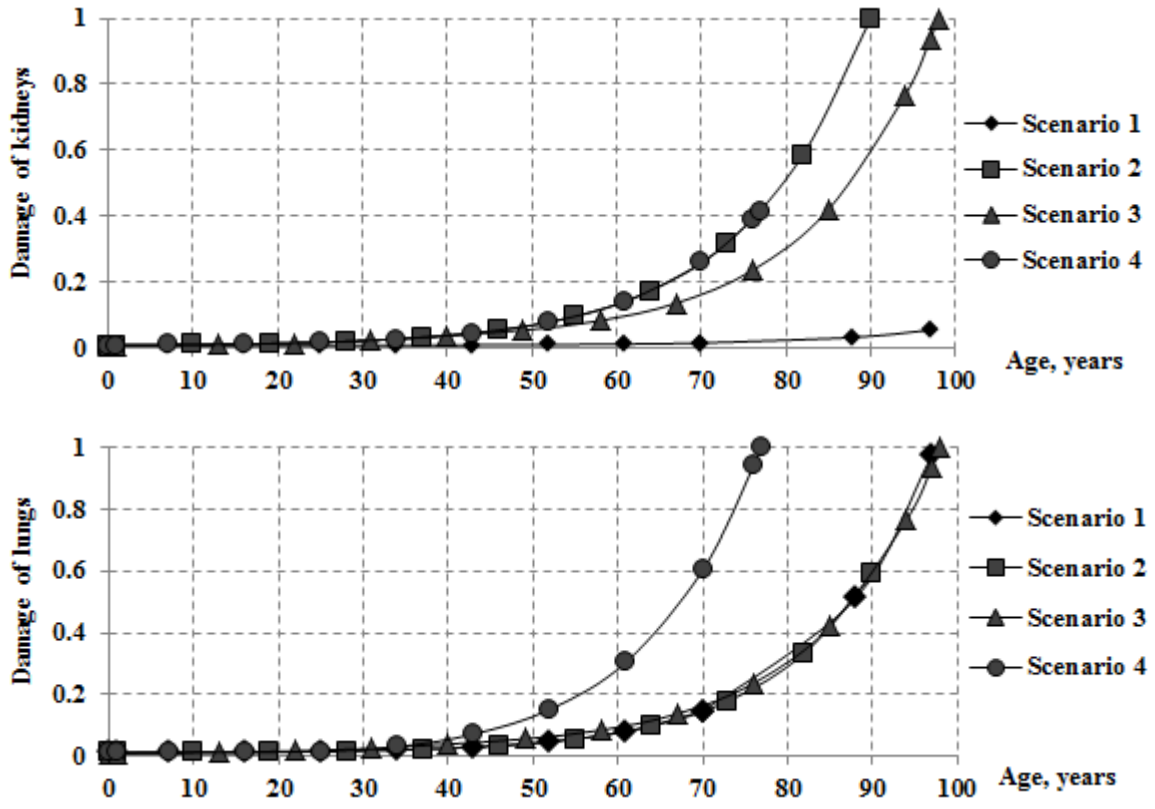

Fig. 3. The graph showing damage of the kidneys and lungs over time.

Obviously, destruction makes a greater contribution to damage development than organ reparation and damage grows uninterruptedly over time. A break in curves in the graph (the end point) corresponds to the moment of time when damage in either organ reaches 1 (when an organ is totally unable to perform any of its functions, it means death of the body as a whole). For example, the scenario 1 covers only natural ageing and recovery, therefore, such a state is reached considerably later than in the scenario 2 where exposure to lead occurs. The scenario 3 involves periodical treatment of kidney diseases; therefore, the damage curve grows slower than in the scenario 2 where no treatment is considered. In the scenario 4, damage to the lungs grows drastically from the moment a negative lifestyle factor starts producing its effects (smoking).

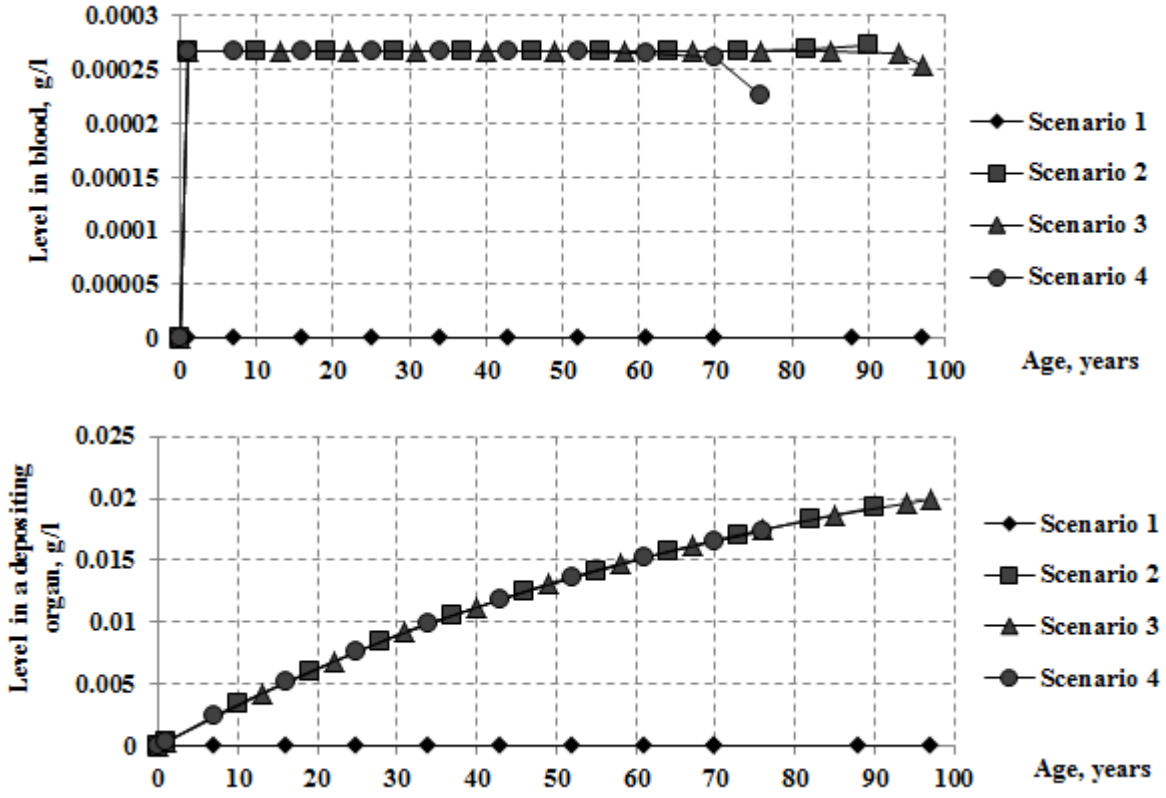

Fig. 4. The graph showing changes in levels of a toxicant in blood and the musculoskeletal system over time.

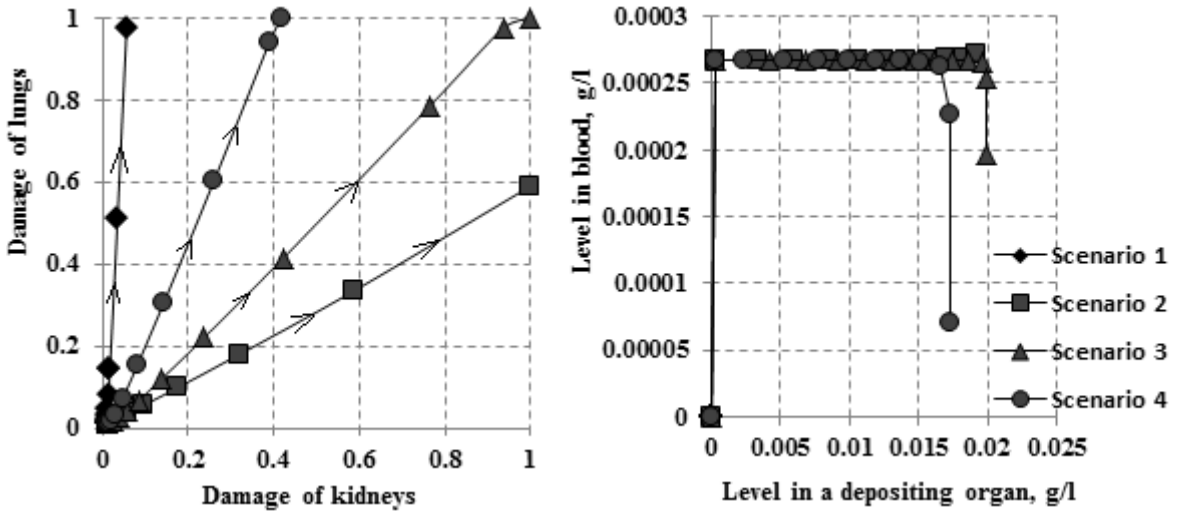

Fig. 5. Phase trajectories for the analyzed scenarios.

Figure 4 provides graphs showing changes in levels of the analyzed toxicant in blood and a depositing organ. The lead level in ambient air is constant in the scenarios 2–4; due to it, the lead level in blood also remains constant until damage of organs does not grows drastically. A constant growth in chemical levels in a depositing system is evidenced by known data: lead goes on accumulating in bones for many years. The levels of the analyzed toxicant in blood remain stable over a long time within the scenarios 2–4 whereas the rate at which the chemical is entered from ambient air remains significantly high even when there are functional disorders in the lungs. In the scenarios 3 and 4, the level of the toxicant affecting

the kidneys goes down since the entry of this chemical through the lungs decreases according to the kinetic model.

Figure 5 shows phase diagrams for the analyzed scenarios. The chemical levels deviate from the equilibrium state due to changing damage of the organs responsible for entry and excretion of harmful chemicals.

5. CONCLUSIONS

This study describes a mathematical model able to predict how functional disorders would develop in organs and systems of the human body under exposure to environmental factors. To describe evolution of the human body adequately, it is necessary to create multi-level models. This article focuses on the structure and relationships within the macro-level model. To close it, we had to introduce some ‘plugs’ at those sections of it where ‘inputs’ from meso-level models would be located in future. The created model considers individual peculiarities, systemic interactions between different organs and the environment, neuro-immune-endocrine regulation, and some other important processes in the human body.

The numeric solution to the system of equations was accomplished by using finite-difference schemes; to approximate the first derivatives over time, the right finite differences were used. The solution to the system of equation was implemented in a software module able to compute damage of separate systems in the body depending on intensity of affecting factors. The model parameters were identified for several affecting factors in order to show qualitative results that allow assessing influence of the environment on human health.

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