Health as a space-time continuum

Anatolii Gozhenko[1], Viktor Biryukov[2], Olena Gozhenko[1], Walery Zukow[3]

[1]State Enterprise "Ukrainian Research Institute for Medicine of Transport Ministry of Health of Ukraine", Odesa, Ukraine
[2]Department of Social Medicine, Public Health and Medical Law of Odesa National Medical University, Odesa, Ukraine
[3]Department of Spatial Management and Tourism, Faculty of Earth Sciences, Nicolaus Copernicus University, Torun, Poland

Corresponding author: Walery Zukow, e-mail: w.zukow@wp.pl

Abstract

The purpose of work is to quantify the changes of the organism functional reserves during the successive phases of the human health Space-Time Continuum (STC) on the basis of postulates of reliability complex systems theory. The study is devoted to the problem of age-related human involution, which is evaluated not from the causal, but from the kinetic point of view.

The analysis of 10 most important basic life support systems of human body — cardiovascular (CVS), respiratory (RS), nervous (NS), digestive (DS), endocrine (ES), immune (IS), excretory (EXS), brain (BS), musculo-skeletal (MSS), hematopoietic (HS) was carried out.

Based on this analysis two levels of ensuring the reliability of organism's work were revealed: sequential and parallel.

The system of logical equations for reduced sequential system is:

Ys1 = CVS ⋀ RS ⋀ BS, where ⋀ is the notation for the conjunctions of set elements.

The system of logical equations for the reduced parallel system is: Ys2 = NS ⋁ DS ⋁ ES ⋁ IS ⋁ HS ⋁ EXS ⋁ MSS, where ⋁ is the disjunction of the scheme elements.

Visualization of human STC changes the concept of the kinetics of age-related changes in the organism and the role of determinants of health as a stable factor accompanying a uniform, smooth transition from the most pronounced functions of the body to their gradual extinction.

For human STC is formulated the following regularity kinetics of involutionary processes: *after 30 years of age in the human body morphological changes regress in arithmetic progression, and the functions of organs in a geometric one.*

Assumption of health as a state redundancy of functions is suggested.

Key words: space-time continuum; the theory reliability of complex systems; integrated assessment of health; redundancy of functions; risk management.

1. Introduction

The present study investigates the properties the Space-Time Continuum (STC) of human health from the standpoint of health concept reliability of complex systems (RCS). It is known that human life characterized by different periods of activity morphogenesis, maturation and functioning of organs and body systems, speed evolutive and involutive processes [21]. There are many theories of aging the human body [4, 11, 12], anyway explanatory gradual involution physiological mechanisms for human adaptability to the environment. Based on these theories was put forward "recovery" concept [11, 12, 30], which, despite their consistency did not bring the expected progress in the extension of high-grade bio-social life throughout its entire length.

Determination of human health by WHO experts as "a state of complete physical, mental and social wellbeing and not merely the absence of disease or infirmity" [23] are not able to cover the entire period of human life. It applies only to people young and middle age, as for elderly, senile elderly and needed substantial amendments within the meaning of the term "total well-being" in the background of a number of serious physical, mental and social «age-related» losses.

Human health as his phenotypic attribute, as a given, fixed in time, changing together with the certified person's age. Health is regulating and limiting factor of each individual life, it is - the conditions and processes of life support. As a

condition, it has a number of strict limitations and physiological determinants. As the process - it is extremely plastic, has a clear chronology sequence biophysical, biochemical and biosocial events developing in time and space (in STC) for certain scenarios. These scripts are different from the processes of inanimate matter: their realization, in addition to exchange substances, is carried out with the assistance of self-processes, self-regulation and self-replication [22].

STC man - the biosocial continuous chain of events accompanying and forming individual structure and the speed of the life cycle in time and space. Picture of STC, as the enclosed space of the individual, his temporary continuous capsule comprising all elements of existence, covering the prenatal and postnatal periods of life, allows you to create and develop new approaches to health biometrics.

The relevance of the topic due to the incompleteness raised STC human health theory, as well as the intensification contradictions in the views on the way and the possibility to extend the active period of life.

The purpose of this paper is to measure changes in the functional reserves the body during successive phases of STC, based on the postulates of theory RCS.

The methods of biostatistics, mathematical logic, conceptual approach, the risk management requirements of ISO standard 31010: 2011 and International standards for determining the reliability of the technique GOST 27.002-89 [3, 18].

2. General concepts

In this study, the standard terminology [3] was adapted in relation to functions the human organism in the following interpretation.

Reliability is a property of the body's system of organs to maintain in time, within the established values, all parameters that provide the required functions in physiological conditions.

Note. Reliability is a complex property that depending upon the host systems and their metabolic conditions may include additional parameters: reliability, durability, and the possibility of correcting or certain combinations of these properties.

3. Assessment of the state

Normal state (good state) - a state organ or system meets all the clinical and laboratory criteria of a healthy body, accepted in medicine.

Fault, faulty state - a state organ or system in which the identified non-compliance for at least one of the criteria for a healthy body.

Up state - state organ or system, where in the values of the parameters characterizing the ability to perform the predetermined functions corresponding to physiological norms.

Down state - state organ or system in which the value of at least one parameter indicative of the ability to perform specified functions, does not correspond to physiological norms.

Note. For complex objects may divide their inoperative states, highlighting partially inoperable varying degrees. In this case, the object under study is able to partially perform the required functions.

Failure - the event is in violation of an efficient condition of organ or system.

Failure criterion - a sign or set of signs of violations of the working condition of the organ or system, installed in the medical regulations.

Failure effect - phenomenon, processes, complications, events and status, due to the appearance of organ failure or system.

Sudden failure - refusal characterized the abrupt change in the value of one or more parameters of activity or organ system.

Gradual failure - the failure resulting from gradual changes in the values of one or more body parameters or system.

4. Main part

According to the current concept, the basis of preserving the population's health should be based on preventive measures, warning the emergence of communicable and non-communicable diseases [13, 15, 16, 17, 19, 21]. At present, it is customary to consider human health through biosocial determinants, which include: genetic potential, phenotypic potential, professional health, reproductive health, anthropogenic factors, socio-economic factors, nutrition.
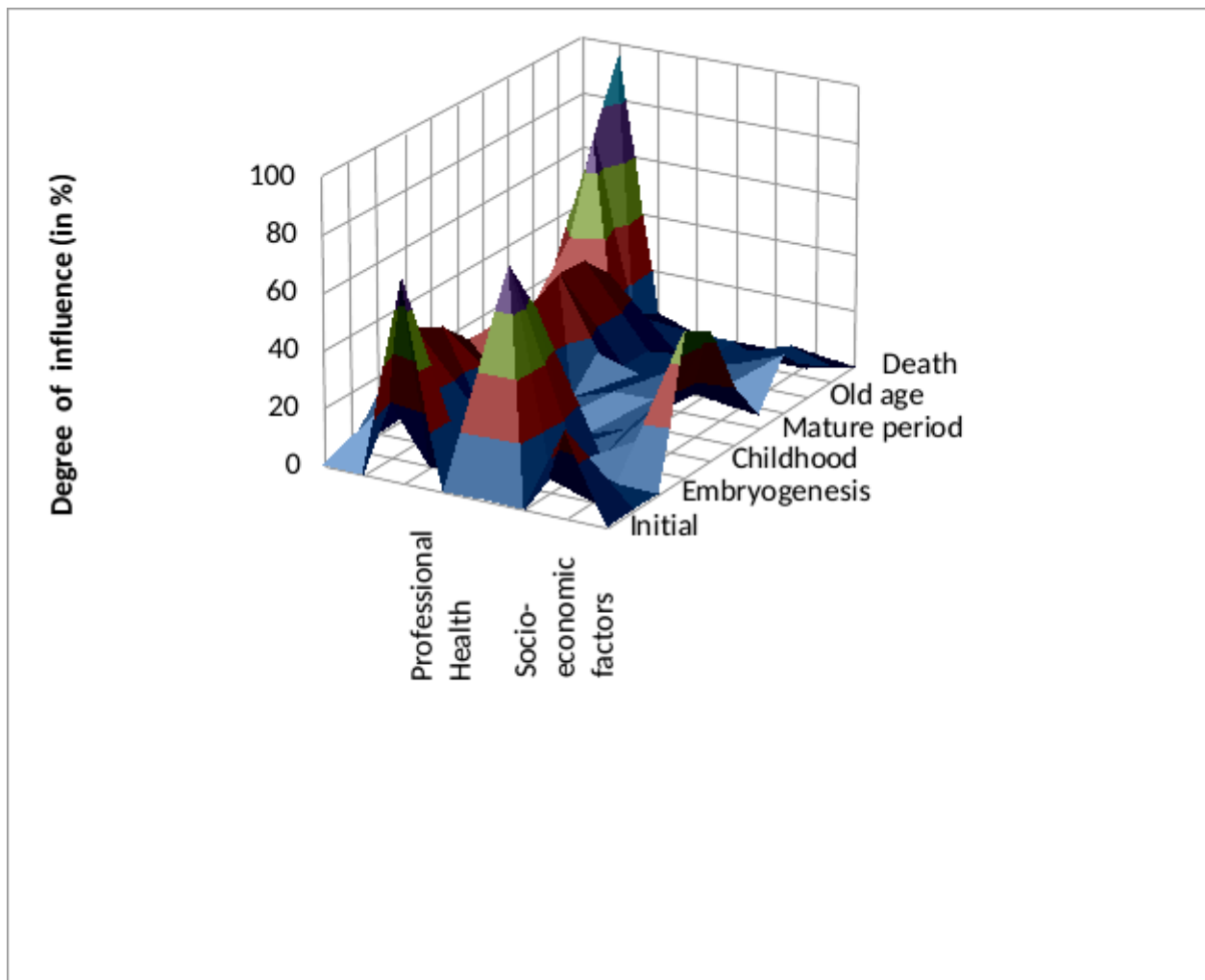
Figure 1. Space-time model of human health (*Gozhenko, Biryukov, 2017*)

Figure 1 shows a graphical reconstruction the STC on the basis a comparison degree of influence determinants health on each stage of human life (in percents): initial environment, conceiving, embryogenesis, newborn period, childhood, juvenility, mature period, elderly age, old age, longevity, death. For this purpose, were used determinants of human life, reflected in numerous WHO materials and research groups [31, 32, 33]. When the graph was constructing, we proceeded from the hypothesis that the sum of all determinants for each stage of life in prenatal and postnatal periods is 100%.

The study age features of functioning the human organs and systems is widely discussed. The prevailing view is that the functions of organs and systems gradually deteriorate with age. However, modern analytical approaches to the study of complex multilevel systems make it possible to verify the degree of reliability of such representations.

Table 2 shows the number of processed data in the literature [3, 4, 5, 10, 11, 17, 27, 28] characterizing the activity of various organs and systems in age aspect.

These data can be used to calculate the reliability of basic life support systems (BLSS) human throughout the STC.

Analyzed BLSS not equal in the risk of sudden or gradual failure, durability and correction capabilities. Based on the concepts RCS, it can be assumed that the multicomponent human life support system has two levels.

Table 2. Characteristics of the main functionality the basic life support systems (BLSS) person in the age aspect

Basic life support systems	Functionality BLSS					
	Age periods (years)					
	30	**40**	**50**	**60**	**70**	**80**
CVS	1.00	0.90	0.85	0.70	0.65	0.50
RS	1.00	0.85	0.70	0.60	0.50	0.33
NS	1.00	0.96	0.90	0.86	0.80	0.70
DS	1.00	1.00	0.96	0.94	0.92	0.80
ES	1.00	0.95	0.90	0.85	0.80	0.75
IS	1.00	0.80	0.50	0.35	0.20	0.15
EXS	1.00	1.00	0.90	0.80	0.70	0.60
BS	1.00	1.00	0.95	0.90	0.80	0.75
MSS	1.00	0.95	0.90	0.70	0.60	0.55
HS	1.00	1.00	0.90	0.80	0.60	0.40

Notes: **CVS** - cardiovascular system; **RS** - respiratory system; **NS** - nervous system; **DS** - digestive system; **ES** - endocrine system; **IS** - immune system; **EXS** - excretory system; **BS** - brain system; **MSS** - musculoskeletal system; **HS** - hematopoietic system (in accordance with the structure by calculating the reliability.

Visualization of STC (Figure 2) through the prism of age-related changes in BLSS creates a new perception of age-related kinetics. Smooth age-related extinctions the organs functions, at their casual combination; mutually potentiate each other, like an avalanche.
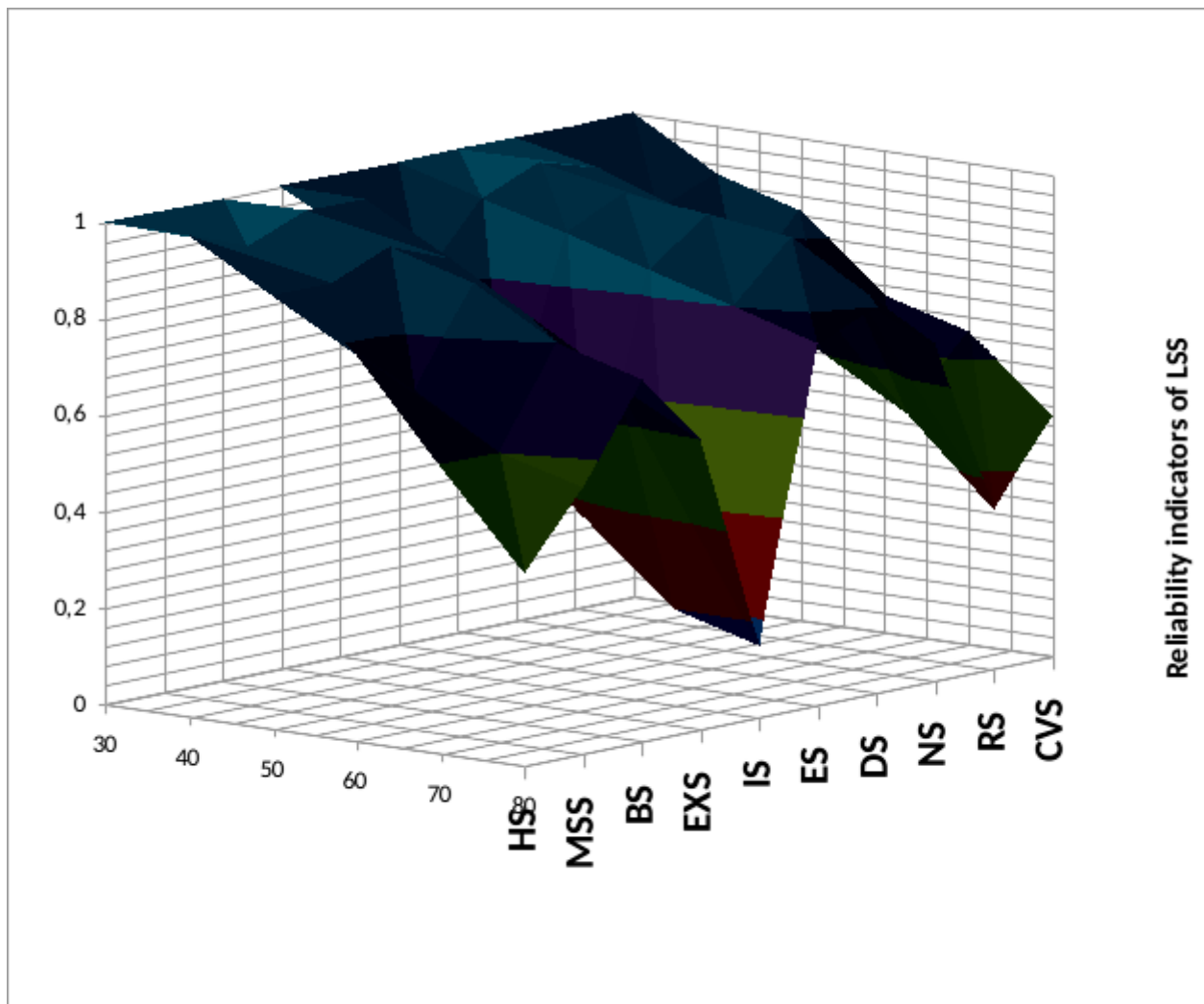
Figure 2. Graphic reconstruction of age changes in indicators reliability of BLSS in the human body. For notations, see Table 2.

Analyzed BLSS not equal in the risk of sudden or gradual failure, durability and correction capabilities. Based on the concepts RCS, it can be assumed that the multicomponent human life support system has two levels.

First level represented by a block of successive elements where the failure of any of them leads to failure BLSS in general. **Second level** includes parallel block elements BLSS when the failure occurs in case of failure of all elements (Figure 3).

The first level should be attributed BLSS, failure of activity which occurs immediately vital stop or condition is incompatible with life (heart attack, stroke, etc.). CVS, RS, BS Probability (P) uptime of each these systems is denoted by Pcvs, Prs and Pbs, respectively. For this level, by S. Lem [14], in which, despite the presence the entire hierarchy of compensatory mechanisms sufficiently "harmless" unit factor can bring the whole system the body to a sudden failure, characterized by "minimal structural redundancy", where, despite the existence a

hierarchy of compensatory mechanisms, rather "harmless" single factor is able to bring the entire system to a sudden failure and death. According to the RCS-concept systems like rigid body typical for regulating vital functions consistent structure.
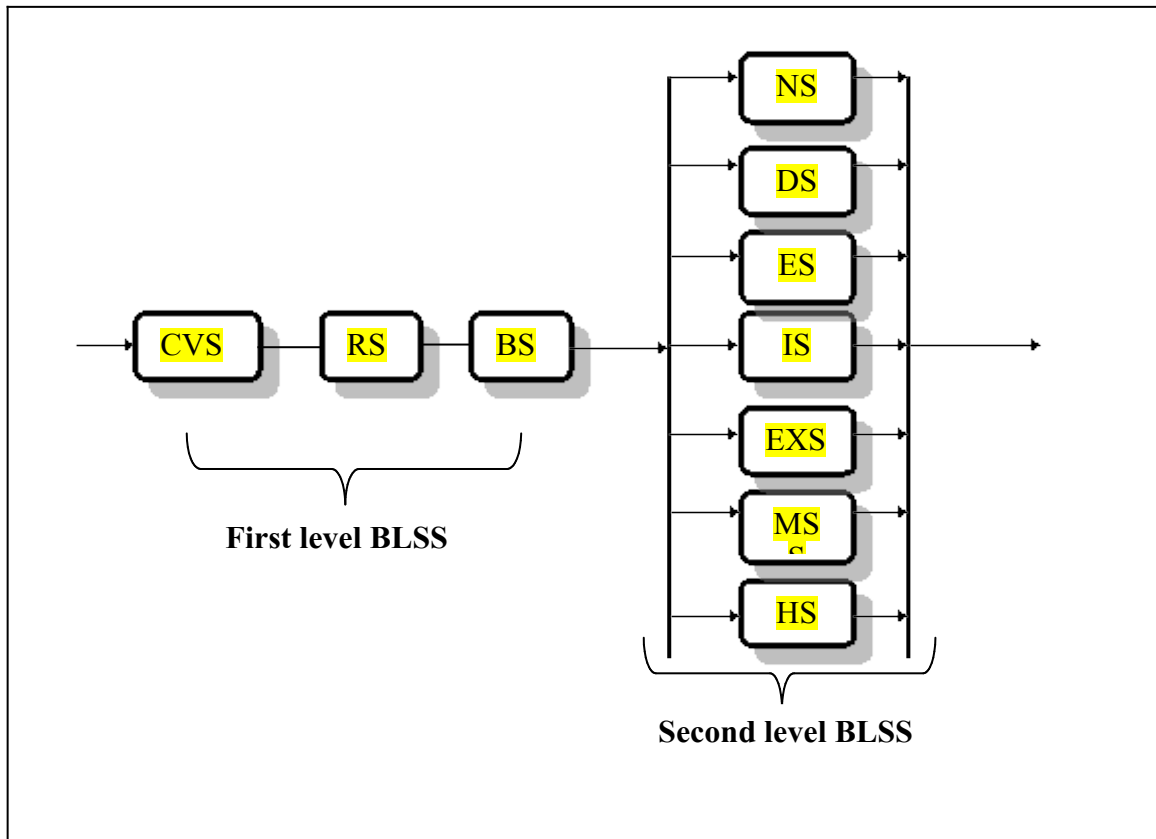

Figure 3. Sequential structure the first level and parallel structure the second level of the human BLSS. For notations, see Table 2.

The system of logical equations for the sequences of the following systems:

$$Ys1 = CVS \quad RS \quad BS \tag{1}$$

where   - marking elements, conjunctions set.

Based on this representation, the combined probability of (Ps1) uptime first level will be described by the following equation:

$$\mathbf{P}s1 = \mathbf{P}cvs \times \mathbf{P}rs \times \mathbf{P}bs \tag{2}$$

The second level basic life support systems can be represented by a parallel system. System logic equations for the parallel system shown is as follows:

$$Ys2 = NS \quad DS \quad ES \quad IS \quad HS \quad EXS \quad MSS \tag{3}$$

where   - disjunction circuit elements.

Sum probability (**P**s2) uptime second level will be described by the following equation:

$$\mathbf{P}s2 = 1 - (1-\mathbf{P}ns) \times (1-\mathbf{P}ds) \times (1-\mathbf{P}es) \times (1-\mathbf{P}is) \times (1-\mathbf{P}hs) \times (1-\mathbf{P}exs) \times (1-\mathbf{P}mss) \tag{4}$$

Statistical and graphic processing table data by the above formulas is shown in Figure 3.
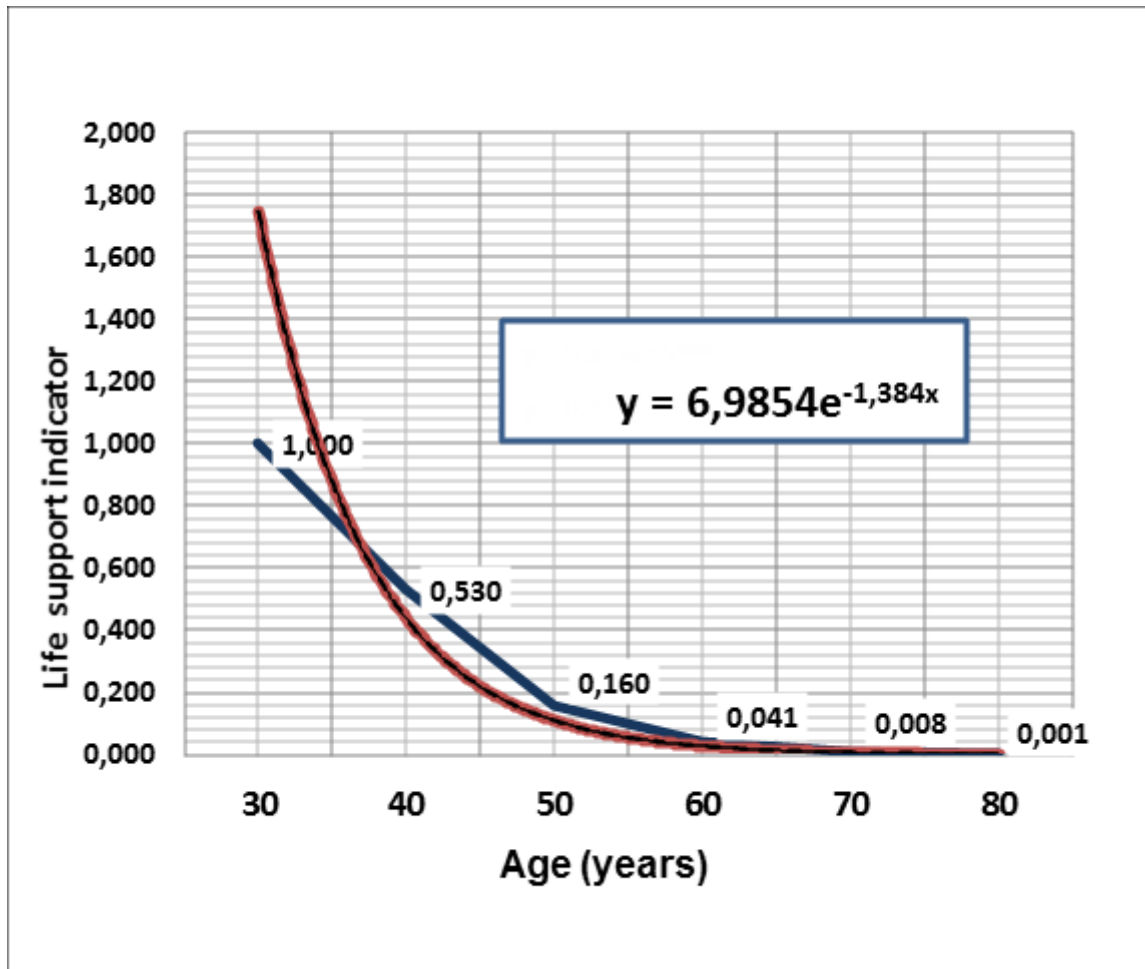

Figure 4. An example of the nonlinear relationship between inhibitions of BLSS and human age.

Data on changes in the overall life support systems for human STC, show a rapid depletion of human resources after 30 years of age. This depletion is not the character of «gradual failure», and has an exponential curve of extinction functions. For 40 years it retained approximately 60% to 50 years - 20% by 60 years and up to 4% of the total capacity of the system 30 years of sustaining life. This indicates substantial redundancy functional reserves, which has a human body by 30 years of age. Its potential exhausted only to 80-90 years of life.

In the figure, as well as an image of human STS indicated the presence of irregularly time-varying parameters, the presence of the rapidly emerging reflecting kinetics different from arithmetic progression. Their events described geometric progression. How valid revealed statistical regularity of macroorganism in respect of its constituent organs and systems?

Consider the issue of conservation and extinction functions with age, as an example of such a body as the kidney, characterized by its extremely complex and hierarchical structural and functional organization.

At what point we can talk about the occurrence of renal failure associated with age-related involution?

More than 20 years of experience (Gozhenko, et al., 2001, 2009, 2015) study the circulatory features nephron glomerular filtration and in various pathological conditions showed high diagnostic relevance indicators of renal functional reserve (RFR) [1, 2, 23, 24]. First-term RFR was introduced in J. Bosch et al in 1983 G. [26]. RFR defined as the difference between the maximum (stimulated) and basal values glomerular filtration (GF) [1, 2].

On the usefulness of renal function is influenced by both the cortex and medulla. Rooted in practical public health picture of chronic renal failure (CRF) is based mainly on the GF indicators stored the amount of viable nephrons, azotemia degree [25].

The study of the RFR in various pathological conditions revealed that long before the clinical and para-clinical symptoms are a gradual depletion of the RFR [23, p. 176-177]. In a healthy person, the RFR in two times exceeds the needs of the whole organism at rest. CRF - the state of irreversible damage to kidney homeostatic functions related to the inclusion in the process of all elements of the nephron. In CRF filtration the kidneys ability was reduced to 25% or less of age norm. CRF does not appear immediately but is caused by the accumulation of partial dysfunctions. Chronic renal failure manifested in the number of permanent syndromes: azotemia or uremia; anemia; water and electrolyte imbalance; disturbance of acid-base state (typical metabolic acidosis); arterial hypertension; hormonal influences; osteodystrophy; violation of hemostasis; violation of cellular immune functions [8].

Already in the 1978 Guide for pediatricians (Arneil G. et al.) [25] observed the nonlinear relationship between the morphological and clinical impairment of renal function.

As a multifunctional organ with a number of independent functions and complex morphological and functional structure, kidney belongs to the second type of structural reliability. Its functions are implemented in parallel processes (Figure 5).

It is known [7, 9; 10, p. 568; 26] that GFR rate is reduced after 40 years by 1% per year (approximately 0.8 ml / min per 1.73 m^2 annually). A healthy 80-year-old human GFR rate is only 1/2 or 1/3 (50-30%) of 30-year filtration. Renal blood flow is reduced from 649 ml / min in 40-year old men to 289 ml / min (44.53%) in 80-year olds. Concentration ability in mOsmol/l decreases from 1109 to 882 (79.53%).
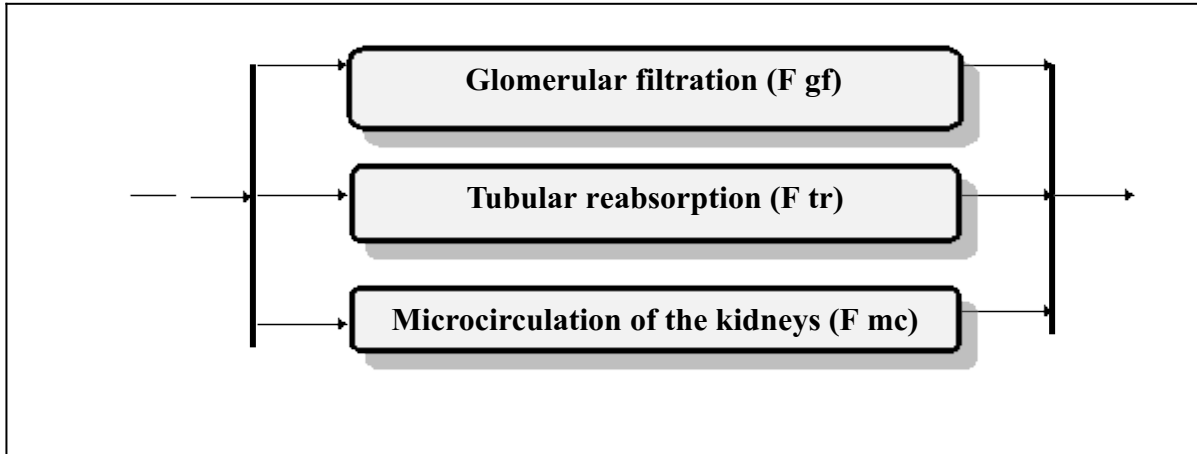
Figure 5. Parallel structures the vital functions of kidneys

The total probability of failure the kidney (**Ps2**), according to formula (4) will be described by the following equation:

Ps2 = 1 - (1 - **F gf**)×(1 - **F tr**)×(1 - **F mc**)   **(5)**

Then the kidney uptime will be as follows:

Ps2 = 1 - (1 – F gf)×(1 – F tr)×(1 – F mc) = 1 - (1 – 0,50)×(1 – 79,53)×(1 – 44,53) = 1 – (0.50×0.21×0.55) = 0.94

The product of (1 – F gf)×(1 – F tr)×(1 – F ms) reflects the time the loss of the kidney function. Putting numerical values corresponding to the age-related changes, we obtain a graphical representation of age-related loss of renal function, reflected in Figure 9.
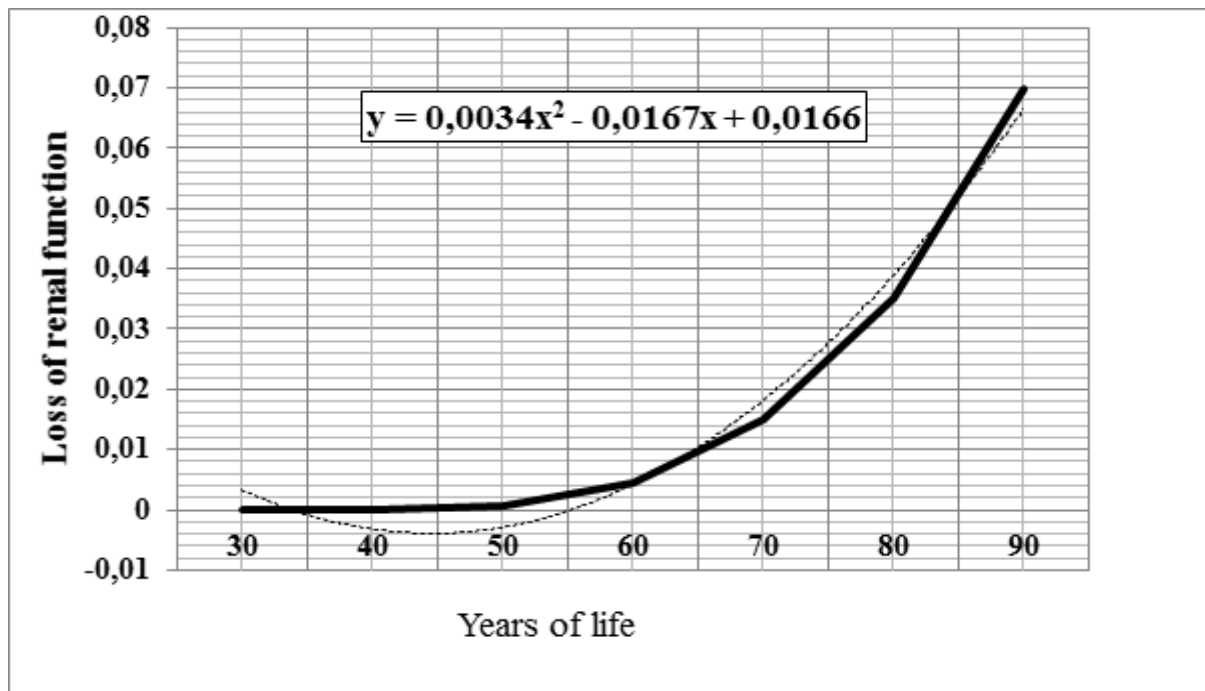

Figure 6. Total loss of renal function associated with age.

Thus, in these examples, we can see that morphologists described "progressive» (gradual failure) involutive change of kidney tissue is accompanied by significant functional impairment of kidney function, which should not be linear, and the progressive exponentially functional process of involution.

7. Conclusion

Developing a model of the space-time continuum, the authors proceeded from the postulate that man is mortal. Throughout its lifecycle always - visible and invisible - there are many and varied risks of exogenous and endogenous nature. Their importance, the significance of the effects, the ability to reduce the negative impacts on the healthy longevity is a subject of attention of several generations of scientists and underlies a number of hypotheses.

Such a common approach allowed to create several theories to explain the reasons for the steady, gradual deterioration of human health with age.

We submitted the data obtained based on the concept of the reliability of complex systems, opening new patterns of kinetics involutional processes that can be expressed in the following words: morphological changes in progress in arithmetic progression, and functions of the organs - in geometric.

The presence of numerous hypotheses to explain the issues from different perspectives involution of the human body, reflecting a lack of basic research in the study of patterns of morphological and functional kinetics, flowing in space and time specific for each individual STC.

On the other hand, they form an illusory picture of the possibility to drastically expand the time interval of man's plentiful life beyond 120 years due to preventive programs. The biokinetic approach based on the theory of reliability the operation complex systems show the need for serious consideration a combination risk factors that can spasmodically worsen the functional state of organism, down to failure of vital systems.

The presence of numerous hypotheses to explain the issues from different perspectives involution of the human body, reflecting a lack of basic research in the study of patterns of morphological and functional kinetics, flowing in space and time specific for each individual STC.

On the other hand, the dominant thinking on the nature of health form an illusory picture of the possibility of extending a full life based on human health and social prevention programs for the prevention of infectious and non-communicable diseases [4, 6, 11].

This ideology permeates hypothesis about the importance of preventive medicine, preventive "molecular dispensary" (Poletaev, Grin'ko, 2012) [17], and predictive medicine [16] and personalized genomics [29,30].

Classical methods for the study of the human body to the morphology of the positions (anatomy, histology), physiology (normal and pathological), biochemistry, biophysics, genetics, clinical disciplines provide numerously, but fragmented material. The concept of human STC may contribute methodology single integrated assessment of human health.

References

1. Gozhenko AI, Kuksan' NI, Gozhenko EA. (2001). Metodika opredelenija pochechnogo funkcional'nogo rezerva u cheloveka. [Method for determining renal functional reserve in humans]. Nefrologija. 5(4):70–73. Russian.
2. Gozhenko AI, Haminich AV, Gozhenko EA. (2009). Funkcional'nyj pochechnyj rezerv: mehanizmy, metodiki opredelenija i diagnosticheskoe znachenie. [Renal functional reserve: mechanisms, methods of determination and diagnostic value]. Nefrologija. 13(3):149. Russian.
3. GOST 27.002-89 (1990). Nadezhnost' v tehnike. Osnovnye ponjatija. Terminy i opredelenija. [GOST 27.002-89 Dependability in technics. Basic Concepts. Terms and Definitions]. [Electronic resource]. [Date 01/07/1990 administration]. Access mode: http://docs.cntd.ru/document/ 1200004984. Russian.
4. Dil'man VM. (1987). Chetyre modeli mediciny. [Four medicine model]. L. Medicina. 288 p. Russian.
5. Dlouhá G, Krshechek I, Natochin Yu. (1981). Ontogenez pochki. [Ontogenesis of kidneys]. L. Nauka. 184 p. Russian.
6. Zhogno YP, Biryukov VS. (2016). Sposib rozraxunku rehionalnyx potreb naselennya u paliatyvnij dopomozi (na prykladi Odes"koyi oblasti): naukovyj tvir. [Method to calculate the regional needs of the population in palìativnìj assistance (for example, Odessa region): scientific work]. Svidotstvo avtorskogo prava tvir nomer 69160 od 14.12.2016. Ukrainian.
7. Zaks MG. (1975). Vozrastnye osobennosti funkcii pochek. Vozrastnaja fiziologija. [Age characteristics of renal function. Age physiology]. Rukovodstvo po fizjologii. [Physiology Guide]. red. VN Nikitin. L. Nauka. 313–329. Russian.
8. Ignatova MS, Vel'tishhev JuE. (1989). Detskaja nefrologija: rukovodstvo dlja vrachej. [Pediatric Nephrology: a guide for physicians]. Medicina. 2-e izd., pererab. i dop. 388-389.
9. Issledovanie velichiny pochechnogo plazmotoka i krovotoka [Jelektronnyj resurs]. Portal iLive.com.ua Rezhim dostupa: http://ilive.com. ua/health/issledovanie-velichiny-pochechnogo- plazmotoka-i-krovotoka_105365i15978.html [Research quantities renal plasma flow and blood flow [Electronic resource]. Portal iLive.com.ua Access: https://goo.gl/2v6QYn. Russian.
10. Issledovanie-velichiny-pochechnogo- plazmotoka-i-krovotoka_105365i15978.html Research quantities renal plasma flow and blood flow [Electronic resource]. Portal iLive.com.ua Access: https://goo.gl/4KWnUR. Russian.
11. Kishkun AA. (2008). Biologicheskiy vozrast i stareniye: vozmozhnosti opredeleniya i puti korrektsii: rukovodstvo dlya vrachey. [Biological age and aging: to be identified and ways of correction: a guide for physicians]. M. GEOTAR-Media, 976 p. Russian.
12. Kondratova NV. (2016). Kak upravlyat' riskami v meditsinskoy organizatsii [How to manage risks in a medical institution]. Zdravookhraneniye. 7. Rezhim dostupa: https://goo.gl/AJsvpe. Access:http://e.zdravohrana.ru/article. aspx? aid = 476592. Russian.
13. Kundiev YuI. (2009). Optymal′na stratehiya zberezhennya zdorov″ya. Peredmova. [The optimal strategy for the preservation of health. Preface]. In Moskalenko VF. (2009). Kontseptual′ni pidkhody do formuvannya suchasnoyi profilaktychnoyi stratehiyi v okhoroni zdorov″ya: vid profilaktyky medychnoyi do profilaktyky sotsial′noyi: monohrafiya. [Conceptual approaches to the formation of a modern preventive strategy in health care: from prevention of medical to social prevention]. K. Avitsena. 11–14. Ukrainian.

14. Lem S. (1968). Summa tekhnologiy. [Sum technologies]. M. Mir. 1968. 344–409. Russian.

15. Moskalenko VF. (2009). Kontseptualni pidhodi do formuvannya suchasnoï profilaktichnoï strategiï v ohoroni zdorov'ya: od profilaktiki medichnoï do profilaktiki sotsialnoï: monografiya. [Conceptual approaches to the formation of a modern preventive strategy in health care: from preventive maintenance of medical to social prevention: monograph] K. Avitsena. 240 p. Ukrainian.

16. Personalizirovannaya prediktivnaya meditsina ili chto takoye Geneticheskaya karta zdorov'ya [Electronic resource]. Pharmacogenetics and pharmakogenomika. 18.11.2014. [Personalized predictive medicine or what is the Genetic Health Card]. Mode of access: https://goo.gl/NM9uKY. Russian.

17. Poletayev AB, Grin'ko OV. (2012). Preventivnaya meditsina: vvedeniye v problemu. [Preventive Medicine: introduction of a problem]. Terramedica. 4:4-8. Russian.

18. Raschot nadozhnosti [Elektronnyy resurs] / Vikipediya. 2016. Rezhim dostupa: https://goo.gl/trcZyz. Calculation of Reliability [electronic resource] / Wikipedia. - 21 August 2016 - Access: https://goo.gl/trcZyz Russian.

19. Romanenko AY. (2009). Nova kontseptsiya protidiï glhat zagrozam Gromadska Health Protection. Peredmova. [A New Concept for Combating Global Challenges and Public Health Threats]. In Moskalenko VF. (2009). Kontseptual′ni pidkhody do formuvannya suchasnoyi profilaktychnoyi stratehiyi v okhoroni zdorov″ya: vid profilaktyky medychnoyi do profilaktyky sotsial′noyi: monohrafiya. [Conceptual approaches to the formation of a modern preventive strategy in health care: from prevention of medical to social prevention]. K. Avitsena. 15–18. Ukrainian.

20. Serdyuk AM. (2009). Find our sogodennya i profilaktichna medicine. Peredmova. [Signs of the present and preventive medicine. Preface]. In Moskalenko VF. (2009). Kontseptual′ni pidkhody do formuvannya suchasnoyi profilaktychnoyi stratehiyi v okhoroni zdorov″ya: vid profilaktyky medychnoyi do profilaktyky sotsial′noyi: monohrafiya. [Conceptual approaches to the formation of a modern preventive strategy in health care: from prevention of medical to social prevention]. K. Avitsena. 19–21. Ukrainian.

21. Spetsifika prostranstvenno-vremennykh svoystv v razlichnykh sferakh mira [Elektronnyy resurs]. Sayt Philo Guide.— 70/5000. [The specificity of the space-time properties in different areas of the world] [electronic resource]. PhiloGuide site. Mode of access: https://goo.gl/wQJR9y Russian.

22. Ustav VOZ: printsipy (2018). [Elektronnyy resurs]. Sayt Vsemirnoy organizatsii zdravookhraneniya. Rezhim dostupa: http://www.who.int/about/mission/ru [WHO Constitution: Principles [electronic resource]. The site of the World Health Organization. Access mode :http://www.who.int/about/mission/ru]. (15.06.2018). Russian.

23. Gozhenko AI, Kravchuk AV, Nikitenko OP at al. (2015). Funktsionalny nirkovy reserve: monografiya. [Functional renal reserve: monograph]. Odesa. Feniks. 182 p. Ukrainian.

24. Arneil GC, Houston JB, Winberg J., at al. (1978). Disorders of the urogenital system In Forfar VJO, Arneil GC Eds. (1978). Textbook of paediatrics. Edinburgh, Churchill Livingstone. 1978. 2nd ed. 859–940.

25. McLachlan MSF. (1978).The ageing kidney. Lancet. 312(8081):143–146.

26. Perneger TV, Klag MJ, Whelton PK. (1993). Cause of death in patients with end-stage renal disease: death certificates vs registry reports. Am. J. Public Health. 83(12):1735–1738.

27. Bosch JP, Saccaggi A, Lauer AW., et al. (1983). Renal functional reserve in humans. Effect of protein intake on glomerular filtration rate. Am. J. Med. 75(6):943–950.

28. Kuo W, Zuo MJ. (2003). Systems with active redundant components. Optimal Reliability Modeling: Principles and Applications. Hobonen. NJ. John Wiley & Sons. Inc. 2003. P. 270–277.
29. Toward precision medicine: building a knowledge network for biomedical research and a new taxonomy of disease. (2011). [Electronic resource]. National Research Council (US) Committee on A Framework for Developing a New Taxonomy of Disease. Washington (DC): National Academies Press (US). 128 p. Retrieved from https://goo.gl/kGPmfC.
30. Biological determinants of health class. 2010. In Public Health Classifications Project. Determinants of Health Phase Two: Final Report. NSW department of health 73 Miller Street North Sydney NSW 2060. NSW Department of Health 2010 SHPN (CER) 100195 ISBN 978-1-74187-461-7. 17-20.
31. Social determinants of health. The solid facts. WHO HFA Policy on Europe: Target 14 Settings for health promotion / Edited by Richard Wilkinson and Michael Marmot/International Centre Health and Society. 1998. 32 P. ISBN 92–890–1287–0.

https://goo.gl/CVfqyk.
32. Walter M. Bortz. (2005). Biological Basis of Determinants of Health. American Journal of Public Health, March 95(3):389-392.