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A Concept of Organism's Functional Integrity and Physical Health Based on Fundamental Limitations of Cells

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Abstract

➢ *Objective:*

The current medical paradigm associates disorders of physical health (PH) with anatomical and functional abnormalities of organs. To diagnose functional disorders, the values of the patient's measured life indicators should be compared with the average values of similar indicators in control populations (i.e., healthy and sick). This approach cannot recommend optimal treatment paths because the originators of slow structural and functional changes in organs are still behind diagnostic technologies. To overcome these limitations, an alternative paradigm is required.

➢ *Methods:*

Systems analysis and evolutionary approach.

➢ *Results:*

A new concept of integrative physiology and a new paradigm (NP) of PH's assessment are proposed, based on an understanding of the shortcomings originating from biophysical and physiological mechanisms of cell life support.

NP considers PH as an evolutionary phenomenon that appeared due to the necessity for specialized cells (SCs) to coexist in a multicellular organism (MO) that exists in an unstable environment. In MO, every SC does provide its basic functions (metabolism, cell cycle, and reactivity). The necessary substrates can be obtained from the close intercellular fluid environment (IFE) that contains metabolites of SCs. None SC consumes its metabolites (wastes), but certain metabolites, capable of stimulating or inhibiting life in other types of cells, functionally integrate them as a physiological multicellular loop (PML). Multiple PMLs provide the functional integrity of MO. However, the SC is not an ideal element to continuously play its roles in PMLs: the stimulation alters the values of SC's cytoplasmic parameters and impairs SC's basic functions. This creates risks of death for the impaired SCs and functional disintegration of PMLs, including organs and MO. To minimize risks, every stagnated SC, competing for common but limited substrates in IFE with other cells, must adequately increase its sucking ability. One of SCs' integral functions is to provide IFE with needed substrates. The efficiency of SCs' coexistence critically depends on their ability to maintain an optimal-like cytoplasm. Across the sieve of evolution passed those MOs that provided an effective solution to this problem. It is shown that a group of internal organs that provide cell life enhances the intracellular mechanisms that govern cytoplasm-genes interaction to minimize the imbalance of anabolic-catabolic transformations. In every specialized organ, the elementary and dynamic functional units determining the current level of output functions are colonies of different SCs, but not SCs.

➢ *Conclusion:*

Fluctuations or trends in the multidimensional parametric landscape of PH reflect the physiology or pathophysiology of SCs' coexistence. The efficiency of coexistence is limited by mechanisms originating: i) vulnerability of cells as structural units to local instabilities; ii) interaction of genes with cytoplasmic factors and roles of internal organs in enhancing adaptive reconfiguring of each SC; iii) internal heterogeneities of common SCs in their colonies. The idea is both a novel concept that

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bridges mitosis, the adaptive reconfiguration of a cell, with the upper-scale physiology, and a key to approaches to personalized prevention, diagnosis, and treatment of non-trivial pathologies of PH.

Keywords: *Adaptation, Prevention, Diagnosis, Treatment, Pathophysiology, Personalized Medicine.*

➢ *Highlights*

- Multicellular organism (MO) does not provide an ideal symbiosis for its specialized cells (SCs)
- SC's basic functions (metabolism, division, and reactivity) are optimal under resting potential (RP)
- During functional integration of different SC's, their RPs alter increasing risks for cells' death
- The quality of physical health (PH) inversely correlates with the number of impaired SCs
- This concept is a key for developing personalized medical technologies

I. INTRODUCTION

The article, presenting a systems view of cells' adaptive responses to induced molecular destruction, is based on the idea that MO is not an object providing idyllic conditions for their cells, but has evolved from a colony of specialized cells forced to coexist in an unstable environment. Till mitosis guarantees certain number of SCs in their colonies, deaths of SCs are not critical. This concept, certain aspects of which are published in [1-3], is opposite to the notions suggesting cells' role is in providing the integrity of MO. At first glance, these notions seem not to ignore the success of cellular physiology. However, they are ideologically close to the anatomical view of the organism. Before considering the main statements of this traditional view, it is worth stressing that cell biologists have not yet proposed a concept capable of integrating the interaction of intracellular mechanisms with multicellular mechanisms in healthy or diseased organisms.

Anatomy views the body as a mechanism, the structural and functional units of which are specialized organs. The utility of this abstraction, visualizing most functions of the body and explaining the roles of organs' structural components in providing these functions, is doubtless. Within the framework of the anatomical view of the body and local structural defects, a lot of pathologies have been explained. Perhaps this was the main reason for the emergence of modern medicine, which is based on the anatomical principles of separating the entire human body into objects (organs or anatomical sub-systems) that are subjects to more in-depth study by narrow specialists. Moreover, the most of medical technologies function in the frame of this view. At the same time, there is a class of slowly (gradually) developing pathologies (with a characteristic functional dissonance between individual organs against the background of the practical absence of visible structural defects), which cannot be explained within the framework of anatomical abstraction. To understand the pathophysiology of such diseases, it is necessary to understand how the function of an organ is related to the functions of its structural elements – specialized cells.

Every MO is a community of SCs and the ultimate goal of systems biologists is to understand rules governing the coexistence of SCs in a dynamic (mainly stochastic) environment [1]. It looks paradoxical that despite the current medicine, identifying more than 20 thousand diseases, did not proposed yet a conventional concept of individual human PH. The medical technologies use statistical methods where exists a virtual object – mean healthy or diseased human – despite every patient is a uniqueness; patient's individual biometrics are resulted of personal genetics, multiple pre-and postnatal adaptive re-building. Physiologists and medical researchers must search for ways out from this paradoxical dead-end.

It seems, since the cellular theory, formulated by T. Schwann in 1839, and especially after R. Virchow's observation that an organism becomes ill only because of abnormalities in certain cells or groups of cells (1855), there is no necessity to stress that the cell physiology plays a crucial role in providing of PH. But it is true only at first glance. The problem is that the founders of the cellular theory suggested that the cell is both the structural and functional unit of every organism. This view is still not revised. Meanwhile, the author of this article has already argued that the cell is not a functional unit of the MO [4]. Therefore, the life support of cells and MO is based on alternative, not yet fully understood mechanisms.

The goals of this article are to argue the following non-trivial statements:

- No cell is "interested" in working on MO because this worsens the quality of the cell's metabolism, maintenance of the cell cycle, and reactivity.
- A big group of organs' slow-developing pathologies affecting PH are consequences of ("a price for") specialized cells' coexistence;
- Understanding limitations connected with specialized cells' dual physiology (to provide internal functions and to function on the integrity of the organism) is a theoretical foundation for developing personalized medical technologies.
- Rethinking certain biological axioms and commons will facilitate achieving these non-trivial goals.

II. RETHINKING CERTAIN BIOLOGICAL AXIOMS AND GENERALIZATIONS

Unicellular life in an unstable environment is a process that lasts till the cell is capable of compensating for the induced destruction of its macromolecules. The quality of a multicellular life depends on the amount of healthy cells in organs. Despite every representative of the biological world displaying nuances of mechanisms

governing life, its understanding can be made easier by using following statements:

- Physicochemical instabilities and biotic invasions are inevitable environmental factors destroying the macromolecules;
- The cell possesses autonomous mechanisms (AMs) that dynamically minimize the imbalance between the mean rates of destruction and biosynthesis of macromolecules;
- Lack of the assortment and concentration of needed substrates in the cytoplasm limits the efficiency of AMs; thus, multicellular physiological mechanisms (MPMs) that create an optimal-like cytoplasm modulate the biochemistry and enhance the efficiency of AMs;
- A part of MPMs is known as internal organs emerged and passed through the sieve of evolution because of their ability to minimize the time during which the catabolism-anabolism imbalance stagnates certain cells;
- As a function of multiple variables, PH inversely correlates with the number of stagnated SCs;
- In MO, every SC is "interested" only in realizing of its basic functions (building organelles, compensating their destructions, and dividing). To maintain these functions, SC needs adequate metabolism and supply of consumables;
- Every organism-scale function of SC's is a complex event containing a phase of SC's integrity loose, and the second phase of structural-functional recovering. Events of the first phase dramatically worsen both SC's ability to maintain its basic functions and functions of organs composed of these SCs;
- Adaptive reactions of SCs to exogenous and endogenous destructive influences help to shorten the time of these dramatic events and mitigate their negative effects;
- The integral effects can be reflected in the dynamics (fluctuations or trends) of life indicators that together forming the multi-parametric space of individual physical (and possibly mental) health;

The recognition of critical manifestations of the dynamics and the search aimed to create methods and technologies for organizing prevention, early diagnosis and adequate treatment of undesirable manifestations are important tasks of physiology and medical science. To facilitate these tasks' solving, several nuances concerning intracellular AMs, functional integrity of internal organs, dynamics of specialized colonies as structural-functional units of organs are considered below.

III. ADDITIONAL EXPLANATIONS AND SPECIFICATIONS

- *Concerning Ams*

The living environment in which our eucaryotic ancestors evolved was not a stable and rich in nutrients and energy. Moreover, certain environmental factors could induce molecular decays critical to breaking the important chains of biochemical transformations in their interim stages. This accumulates certain intermediate products (IPs) in the cytoplasm, worsens the quality of life, and increases the risk of the cell's death. Eventually, some IP1s can penetrate the nucleus while others (IP2s) go out of the cell membrane.

Suppose among IP1s there are several IP1ss capable of stimulating the expression of genes that activate functions of organelles maintaining the biosynthesis of ATP and other macromolecules that were destroyed. Already, such a negative feedback alone could help the stagnated cell to mitigate the anabolic-catabolic imbalance and avoid death. In case among IP1s there are several IP1si, inhibiting the current expression of genes that governing catabolic events, the process of the cell's "recovery" will speed up. So, those unicellular organisms equipped with intracellular autonomic negative feedback mechanisms (AMs) were capable of passing through the sieve of evolution. There is a big probability that such organisms gave rise to MOs to which the humans belong.

Further evolution of MOs created new problems that are mainly solved by employing multicellular mechanisms (MMs) enhancing the limited power of intracellular AMs. In [2], it was argued that MMs include both locally acting mechanisms and internal organs, generally creating an optimal-like cytoplasm environment for minimizing the imbalance between the required rate of biosynthesis and the imposed rate of molecular decay.

- *Concerning Functional Integrity of Internal Organs*

In MO, a cell is a finite object that requires chemicals to service all its mechanisms of life. Question is how under highly dynamics of both cells and parameters of IFE, every SC can be supplied with adequate assortment and concentrations of consumables? Taking into account that an adult human body consists of approximately 30–50 trillion SCs, the answer to this question is not trivial like that the brain organizes this supply. Even if the brain has mobilized 90 billion neurons, optimizing the logistics of distributing consumables is hardly possible and requires too much energy. In a real organism, the brain is responsible for organizing and controlling more critical life events. Evolution accumulated solutions that use less energy but are no less effective. Most of them are based on humoral channels and chemicals capable of dilating or constricting blood vessels. Certainly, under specific conditions that require rapid parrying of dangers, the brain is also involved. However, parallel activation of intracellular mechanisms like AMs eventually lowers the brain investment. Currently, it is known that some AMs provide an up-building of organelles in chronically stagnated cells, while other AMs stimulate mitosis of such cells [5 - 8].

Real internal organs are complex biological constructions built of specialized cell colonies (SCCs). The organ is mandatory "stitched" with a network of blood and lymphatic vessels, and also contains afferent and efferent nerve channels. Vessels supply the consumables and remove metabolites. Nerves quickly adjust the output function of this organ to meet the current needs of cells.

The normal anatomy of the organ ensures its function, but it can also be modulated by the actual number and power of cells in constituent SCCs. Additionally, the modulation depends on how cells are activated (synchronously or asynchronously) [9].

➢ *Concerning Dynamics of SC's' Colonies*

There are at least two reasons to assert that a single cell cannot be a functional unit of an MO such as the human body or the bodies of other animals. First, the body's mass and size incomparably exceed the mass and size of a single cell. With a limited diversity of cells, this is possible if there is a huge number of each type of cell. Second, a single cell cannot function continuously in the interests of the entire organism. Let us clarify these assertions for the human body. An adult human organism contains about 50 trillion cells, while cells' types are about 220. By dividing the first number by the second, one can see that the average number of every SC is approximately 227 billion. This is a huge number. The common specialization cells exist in the form of SCC. Certainly, the number of SCs in different SCCs is not equal. Perhaps, more important are two other aspects: 1. Is this number a constant or does it vary in time; 2. Are the cells of the same SCC identical or not? A little further down, we will see the medical perspectives of knowing the correct answers to this question. For now, let us note how an abstract colony of cells is formed and what factors can affect the functioning capacity of a given SCC.

Mitosis is the mechanism that originates every SCC. The number of SCs in every SCC results from the dynamics of the cell's division and death. So, this number is a variable. To answer the second question above, one has to know the main mechanisms that govern the biology of the cell cycle [6,11]. Cell division has its phases, and every next phase starts only after special checkpoint mechanisms ensure that the current phase is completed. As the completion process needs both a certain assortment of building compounds and their proper concentrations, the longitudes of every phase and the total cell cycle are not fixed parameters but depend on the physicochemical state of the cytoplasm. This state, in turn, depends on the parameters of the near ILE. By generalizing the logic, one can see that a lot of variables at an organism's different scales are modulators of the cell cycle in every SC. The next conclusion from this mechanics is that both in the entire organism and its regions (organs, their functionally associated groups), physicochemical characteristics normally fluctuate. Therefore, by comparing two occasionally taken sister cells, one can find many ultra-structural anisotropies. These differences lead to functional heterogeneities. Typically, sister cells possessing uncial values of thresholds, saturation, and others may display different sensitivity to changes in the parameters of input signals. Already, such nuances cause asynchronous responses of SCs in the SCC. Suppose, in the given SCC, the diapasons of anisotropy are known, and the researcher quantified the given diapason using a finite number of micro-diapasons with the width of Δ, where the differences of cellular parameters are ignored. In this case, a histogram with specific numbers of SCs for every colony can be built. The histogram characterizes the current ability of the SCC to develop a total response to the input-stimulating or inhibiting signal. Only in case the histogram looks like a rectangle, the response is linear. The shapes of nonlinear responses are determined by the character of the histogram [9].

I described these effects because, despite the nonlinearities that abound in biomedical research of macroscopic structures, researchers do not see a causal relationship between the parameters of microscopic structures and the characteristics of macroscopic observation. Meanwhile, it is precisely the fluctuations and trends at microscopic levels that determine macroscopic effects. This knowledge is the key to proper deciphering of curves, which is critically important in medicine.

As the cell is the only object that is capable of providing its reactive ultra-structural adaptation against induced destruction [10], some words will be said about this special modifier of SCC's dynamics. Despite the SC has a genetic program of apoptosis, it is activated in extreme situations. Normally, intracellular AMs use cytoplasmic factors like IP1s to properly rebuild cellular organelles and cope with the negative consequences of energy lack or an insufficient amount of source compounds for activating biosynthetic transformations. Such rebuilding in SCs will reconfigure the above-mentioned histogram in the given SCC. So, AMs, capable of altering the current structure of one or more SCC, that are constructive units of every internal organ, independently alter physiological variables and so-called physiological or biochemical constants traditionally used in assessing specific symptoms of PH's disorders.

➢ *Concerning the Functional Super-System*

The concept of the functional super-system (FSS) was first proposed in [2]. Shortly, FSS functionally integrates intracellular AMs with a group of internal organs. A part of these organs supplies every SC with consumables, while other organs determine physicochemical parameters of cytoplasm. FSS evolved and saved due to its ability to minimize the time interval during which SC is impaired. Normally, FSS, enhancing the adaptive potentials of AMs, provides a multiscale and multilevel optimization of SC's life. The empirical physiology revealed many short or long chains of MPMs, specifically helping the stagnated SC to cope with its impairment. Despite early publications ([1,3,4,11]), which listed several real, not virtual IP2s, here I do not use the commonly accepted terms and limit myself to designating them as IP2s for three reasons. Firstly, in modern physiology and medicine, the absolute majority of such mediator agents are considered specific regulators of the functional state of certain organs. Secondly, there is no certainty that the list of such agents can significantly grow and/or be re-specified. Finally, the producers of such agents are treated as special types of cells. Meanwhile, at least for one such agent, renin (the precursor of angiotensin), there are already a significant number of convincing observations that not only kidney cells, as was primary thought, but almost all types of specialized cells

in a state of induced stagnation activate the renin-angiotensin chain [12,13]. Multiple redundancies of pathways and mechanisms for cells to exit from the dangerous state of stagnation, into which they have fallen for various reasons, are evolutionarily selected effective survival strategies. At least for the circulatory system, these pathways are covered in detail in [11].

IV. DISCUSSION

The human organism, as a community of specialized cells, is studied using systems analysis, engineering, and evolutionary approaches. Novel understandings of both an organism's functional integrity and mechanisms causing non-trivial, slow-developing, and multi-symptom pathologies of HP are the main results of the revision. Several original ideas are discussed in this section.

From the engineers' point of view, the properties of any complex artificial structure are determined by the properties of elements and their spatial configuration. To apply this approach to a human organism, it is necessary to clarify the structural element, its properties, and whether the structural unit is also the functional unit of every multicellular structure, including organs and their systems (digestive, cardiovascular, and others). It was revealed that the SC is the structural, but not the functional unit of an organism. Indeed, organs are the functional units, but this fact itself does not reveal mechanisms altering an organ's geometry and functionality. Thus, the most realistic alternative is that populations (colonies) of SCs are the lowest structural-functional units used in constructs of every specialized organ. Therefore, the dynamics of SCs' colony are originators of the dynamics of organs. In turn, the dynamics of both the number of SCs and the current power of each constituent SC in the colony determine the structural-functional dynamics of SCs.

As multicellular colonies of different types of cells are the structural "bricks" in both organs and physiological loops, the next crucial question is to establish the fundamental properties of SCs, vulnerabilities, and limitations. Every physiological loop includes at least three specialized cell colonies (links): a) receptor, b) central, and c) effector. In some loops, there can be interim colonies. Excitable cells are the basis for most loops: neurons are the most well-known representatives of receptor and central links, while myocytes and secretory cells are often the so-called effector cells (ECs). Therefore, to reveal their vulnerabilities and limitations, we need to recall their fundamental properties. Here, our attention will be focused on four aspects: 1) how the cell forms its resting potential (RP); 2) why RP is necessary; 3) what happens in the cell when invasions essentially alter the value of RP; and 4) whether the alterations can have physiological consequences at the organismal scale.

It is well-known that under specific conditions, a neuron generates an impulse (action potential – AP). The figure below schematically illustrates AP by separating its phases. The red dotted line conventionally illustrates alterations in metabolic rate in different phases of AP.

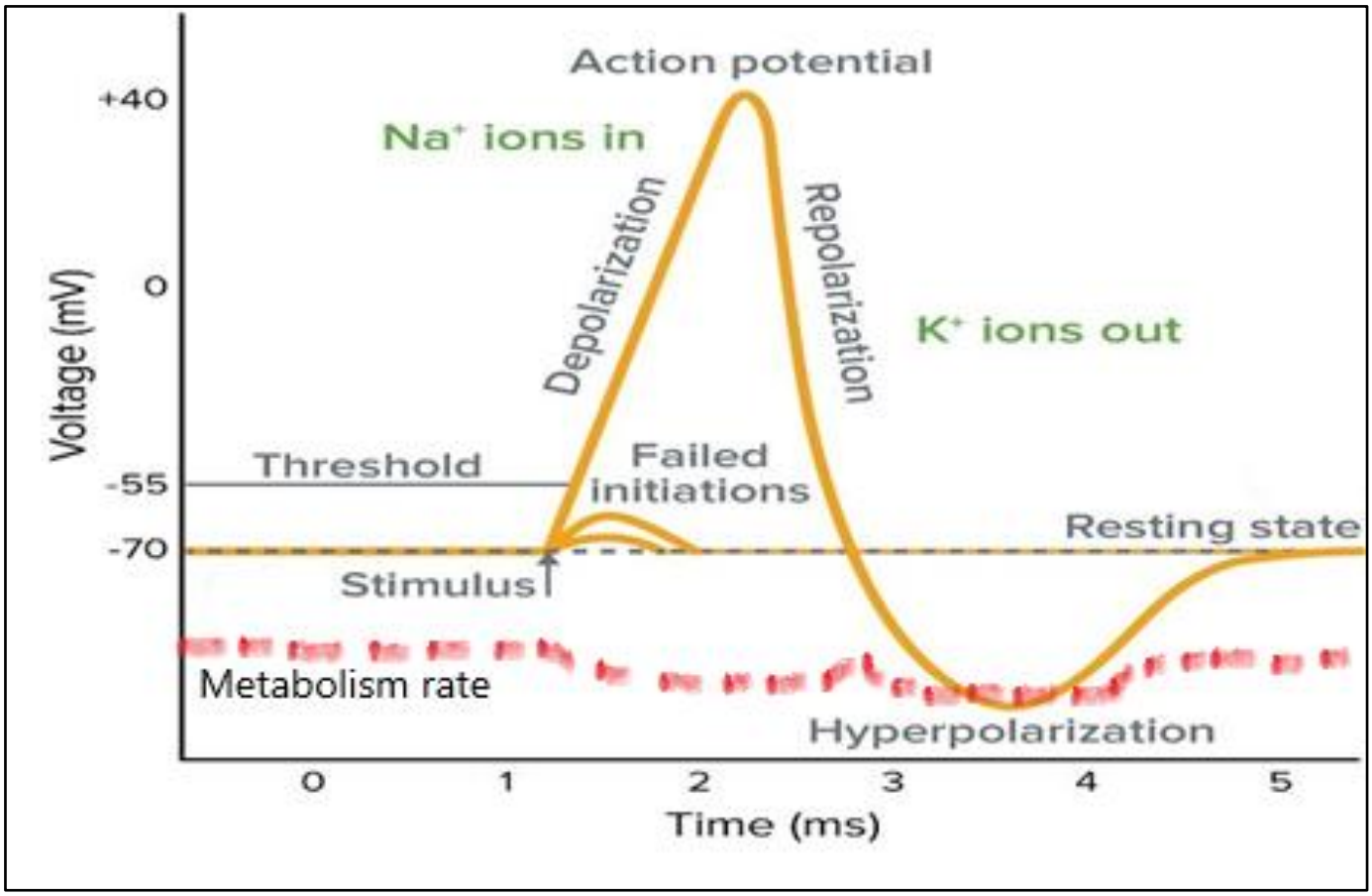

Fig 1 Stylized Picture Illustrating Certain Correlations Between Dynamics of Cytoplasm Electrical Potential and Metabolic Rate (Dotted Red Line) During an Action Potential (AP).

Traditionally, biophysics and physiologists are almost exclusively focused on the explanation of mechanisms that generate AP and provide its propagation through the axon. I do not think it is necessary to describe further effects; they are known to my readers. At the same time, I will focus their attention on two facts: 1) during AP, the metabolism is lowered and restored after RP is restored; and 2) the AP contains a hyperpolarization phase. When the input influence overcomes the neuron's threshold (-55 mV), membrane voltage-sensitive ionic channels open and Na+ ions enter the cytoplasm, reversing its RP to about 40 mV. This opens ionic channels for K+ ions, and due to their higher concentration in cytoplasm, K+ ions leave the cell. The latter process could eventually restore the RP. However, the biomechanics and kinetics of the proteins from which the membrane potassium channels are constructed are such that these channels remain open for some time, causing hyperpolarization. To restore the AP, the neuron is forced to use its ATP molecules. This is one of the fundamental imperfections of both neurons and every SC, limiting the functionalities of animal organisms. Theoretically, this shortcoming can be minimized by using invasions that alter the kinetics of the proteins in the membrane potassium channels. I think a technology capable of providing such an alteration could minimize ineffective energy losses. The second fundamental imperfection of our constituent cells is the vulnerability associated with metabolic stagnation that appears whenever the SC is forced (by stimulating or inhibiting influences that integrate the cell into multicellular functions) to stagnate its metabolism. Changes in the RP can affect cellular excitability, leading to various neurological and muscular disorders. Additional arguments are below.

An important interim conclusion is that in the MO, every SC, being compelled to work both on the MO and provide its basic functions (metabolism, reactivity, and mitosis), cannot guarantee the quality of basic functions until the integrity loss, which happens after a single stimulation, is eliminated.

In every cell colony, the number of SCs is determined by the ratio of SCs' successive mitoses and deaths. This means that the number of SCs in the same colony can vary in time. In other words, the colony is a dynamic object. Most of SCs continue to divide throughout the organism's lifespan. At different periods of life, the physicochemical conditions change, so there is no reason to claim that all daughter cells will start their independent life with the same conditions and achieve the same biological parameters. The latter include size, resting potential, number and size of organelles, characteristics of ion channels of the cell membrane, etc. This list alone allows us to claim that the colony cells will respond to external stimulating or inhibiting effects asynchronously rather than synchronously. It is obvious that the greater the number of synchronous cells, the greater the power of the colony's response. This statement is true for colonies in which cells react to a common influence independently of each other. Colonies formed of the same type of receptor cells, muscle fiber cells, and secretory cells are typical examples of such colonies. Since precisely such excitable cells underlie most manifestations of life in each multicellular organ and organism, it is easy to see how important to know the nuances of the functioning of specialized colonies for understanding physiological or pathological fluctuations and trends on the scale of the organ or organism.

Another aspect to be discussed concerns the functions of intracellular AMs, seen as important chains that determine the adaptive restructuring of organelles to neutralize the negative consequences of induced molecular destruction. Here I see three scenarios. The first one is a passive biochemical adaptation to the accessible assortment of source chemicals for satisfying cellular needs in energy and building compounds. Two other adaptation scenarios based on the cytoplasm-nucleus interaction are reactive. It should be noted that not all stages of this interaction are clear yet. Perhaps, the so-called hypoxia inducible factors in adaptive restructuring, covering both intracellular structures and multicellular specialized organs involved in ensuring increased ATP production under specific conditions of prolonged hypoxia, are a good illustration of the fact that adaptation pathways are diverse and include multi-level mechanisms [19,20]. Thus, I avoided noting specific chemicals mediating stimulation/inhibition of AMs. In my opinion, at this stage of the paradigm shift, it is reasonable to outline this interaction in a "dotted line" by using terms like IP1s and IP2s [1,3].

Cells possess at least three independent mechanisms for adaptation to energy lack [14, 15]. The quickest mechanism activating against acute lack of ATP is based on negative feedback between concentrations of ATP, ADP, and AMP [16]. The slowest mechanism activating against chronic lack of ATP is based on the proliferation of mitochondria and hypertrophy of their inner membrane. The efficiency of both these mechanisms correlates with the assortment and concentration of source chemicals in the cytoplasm or the close intercellular environment. Factors increasing local blood inflows and/or blood concentration of needed chemicals elevate this efficiency [4]. As argued in [1,18], negative feedbacks based on nuclear concentration of IP1s play the initiating role in actualizing biochemical chains that synthesize macromolecular compounds for the mitochondrial up-building. In extreme cases, IP2s activate the multiscale multicellular mechanisms for realizing this up-building. So, increased blood concentrations of IP2s hint that arterial pressure is elevated due to regional or global energy deficiency. In parallel with producing more ATP, the arterial pressure and values of variables (stroke volume, heart rate, total peripheral resistance, venous tone) that maintain the arterial pressure will return to lower levels [11]. This vision of cells' role in determining physiological or pathological values of cardiovascular parameters suggests that, namely, the fight for energy is one of the main causes of arterial hypertension. Moreover, the hypertension may disappear if cells eventually build up a

sufficient amount of effective mitochondria. The third adaptation scenario uses the motility of mitochondrial units (sensitive to oxygen concentration) to maximize the number of these organelles in cytoplasm areas with a higher oxygen concentration. This mechanism is most effective in neurons with long dendrites and axons [7,8].

Excitable cells are not the exclusive group of SCs vulnerable to violations of RP. Non-excitable cells, like most cells in the body, maintain a negative RP due to the unequal distribution of ions across the cell membrane [18]. This imbalance is crucial for various cellular processes, including the movement of ions, nutrients, and waste products. So, every cell uses membrane pumps to provide its specific value of negative RP. Violations of RP can be influenced by various factors, including hormones, signaling molecules, temperature, and pH. The potential difference across the cell membrane drives ion movement, influencing enzymes' activity, protein folding, and overall cellular function. Disruptions to this potential can impair metabolic pathways and cause cellular dysfunction. A significant change in the RP of a non-excitable cell can have profound effects on its metabolism and overall function, potentially leading to cellular dysfunction and even cell death. A decrease in the negative resting potential (depolarization) can disrupt these ion gradients. For example, if the membrane potential becomes less negative, it might become easier for sodium ions to leak into the cell. This potentially disrupts the sodium-potassium pump's ability to maintain the normal ion balance. Changes in ion gradients can directly affect metabolic pathways that rely on these gradients, such as the transport of glucose or amino acids. RP acts as a signal in many cellular processes. Changes in the membrane potential can affect the activity of ion channels, receptors, and other signaling molecules. If a non-excitable cell's membrane potential is significantly altered, it could disrupt the signals it sends or receives, affecting its ability to communicate with other cells and respond to its environment. A change in membrane potential could interfere with the cell's ability to trigger the release of hormones or other signaling molecules, affecting overall tissue or organ function. If the RP is significantly depolarized, the cell might need to expend more energy to restore the normal ion gradients and membrane potential. If the cell's energy reserves are limited, this increased energy demand could lead to energy depletion and cellular dysfunction. Depolarization beyond a certain point could trigger cellular stress responses and even lead to cell damage or death. Depolarization can lead to the opening of calcium channels, which can overwhelm the cell's calcium buffering system and lead to calcium overload, causing cell damage. Even a temporary disappearance of the negative cytoplasmic potential, or depolarization, can significantly alter a cell's metabolism. While a small, transient depolarization might be part of normal cell function, a larger or sustained depolarization can disrupt metabolic pathways and even lead to cell damage or death [18].

NP considers PH a phenomenon associated with the necessity for specialized cells (SCs) to coexist in a multicellular organism (MO) existing in an unstable environment. Our unicellular ancestors, to provide their basic functions (metabolism, cell cycle, and reactivity), were equipped with mechanisms that maintain an optimal-like cytoplasm despite an unstable outer environment. In MO, such cells gave rise to SCs that also provide their basic functions, but in fundamentally new conditions: an intercellular fluid environment (IFE) containing metabolites of SCs appeared. Certain metabolites that stimulate or inhibit life in specific SCs functionally integrate these cells as a physiological multicellular loop (PML). Multiple PMLs provide the functional integrity of MO. However, every stimulation of an effector SC alters the values of cytoplasm parameters and stagnates its basic functions. This creates a risk of death for the stagnated SCs. To minimize the risk, every stagnated SC, competing for common but limited substrates in IFE with other cells, must adequately increase its sucking ability. One of SCs' integral functions is to provide IFE with needed substrates. So, the coexistence dilemma of SCs is how to optimize both their work on itself and the work on MO. Across the sieve of evolution passed those MOs that provided an effective solution to this dilemma. It is shown that a group of internal organs that provide cell life minimizes the negative consequences of this dilemma. Moreover, it is argued that colonies of different SCs but not individual SCs, are functional and dynamic units determining the current level of every three-dimensional specialized organ's functions. At any given time, the functional capacity of a colony correlates with the number of more powerful SCs, and the capacity of the output function of an organ correlates with the capacities of the constituent colonies. This view of the dynamics of colonies explains the instability of the parametric landscape of PH.

V. CONCLUSION

To solve problems arising in the current medical paradigm, including PH, the human organism is revised using systems analysis, engineering, and evolutionary approaches. The main result of the analysis is a novel understanding of an organism's functional integrity and causes of non-trivial, slow-developing, and multi-symptom pathologies of HP. A new paradigm (NP) of PH's assessment is proposed, based on an understanding of the main roles of cellular mechanisms in integrative physiology.

Fluctuations or trends in the multidimensional parametric landscape of PH reflect the physiology or pathophysiology of SCs' coexistence. The efficiency of coexistence is limited by mechanisms originating: i) vulnerability of cells as structural units to local instabilities; ii) interaction of genes with cytoplasmic factors and roles of internal organs in enhancing adaptive reconfiguring of each SC; iii) internal heterogeneities of common SCs in their colonies. The idea is both a novel concept that bridges mitosis, the adaptive reconfiguration of a cell, with the upper-scale physiology, and a key to approaches to personalized prevention, diagnosis, and treatment of non-trivial pathologies of PH.

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REFERENCES

[1]. Grygoryan, R.D. (2025). Mechanisms Dynamically Shaping the Multi-parametric Landscape of Human Physical Health Journal of Medical Discoveries, 2025, RPC Publishers, 2(1); 1-10. https://www.doi.org/rpc/2025/rpc.jmd/00209.

[2]. Grygoryan, R.D., Sagach, V.F.(2018). The concept of physiological super-systems: New stage of integrative physiology. Int. J. Physiol. and Pathophysiology: 9,2,169-180.

[3]. Grygoryan, R.D. (2019). The Optimal Coexistence of Cells: How Could Human Cells Create The Integrative Physiology. Journal of Human Physiology.1 (01):8-28. doi: 10.30564/jhp.v1i1.1386.

[4]. Grygoryan, R.D. (2024). Cells are the solely reactive structures originating internal driving forces of organism's adaptation to external/internal shifts. Danish Scientific Journal, 88, 26-33, https://doi.org/10.5281/zenodo.13884427.

[5]. Hawley, J.A., Hargreaves, M., Joyner, M. J., Zierath, J. R. (2014). Integrative biology of exercise. Cell. 159(6), 738 - 749. https://doi.org/10.1016/j.cell.2014.10.029

[6]. Finkel, T., Hwang, P.M. (2009). The Krebs cycle meets the cell cycle: Mitochondria and the G1–S transition. Proc Natl Acad Sci USA. 106(29).

[7]. Hardie, D.G., Ashford, M.L. (2014). AMPK: regulating energy balance at the cellular and whole body level. Physiology (Bethesda).29(2):99–107.

[8]. Eirin, A., Lerman, A., Lerman, L.O. (2018). Enhancing Mitochondrial Health to Treat Hypertension. Curr Hypertens Rep.,20,10,89. doi: 10.1007/s11906-0180889-4.

[9]. Grygoryan, R.D. (2012).The energy basis of reversible adaptation. New York, Nova Science, 253p., ISBN 978-1-62081-093-4.

[10]. Morgan, D.O. (2007).The Cell Cycle: Principles of Control. London: New Science Press.

[11]. Grygoryan, R.D.(2017). The optimal circulation: cells contribution to arterial pressure. N.Y.: Nova Science, 287p. ISBN 978-1-53612-295-4.

[12]. Nakagawa P, Gomez J, Grobe JL, Sigmund CD.(2020). The renin-angiotensin system in the central nervous system and its role in blood pressure regulation. Curr Hypertens Rep.;22:7.

[13]. Rocha NP, Simões e Silva AC and Teixeira AL (2021) Editorial: The Role of the Renin-Angiotensin System in the Central Nervous System. Front. Neurosci. 15:733084. doi: 10.3389/fnins.2021.733084.

[14]. Hardie, D.G. (2018). Keeping the home fires burning†: AMP-activated protein kinase. J. of The Royal Society Interface. 15, 138. https://doi.org/10.1098/rsif.2017.0774.

[15]. Langendorf, C.G, Kemp BE. (2015). Choreography of AMPK activation. Cell Res. 25:5–6. doi: 10.1038/cr.2014.163.

[16]. Jeon, S.M. (2016). Regulation and function of AMPK in physiology and diseases. Exp Mol Med. 48(7): e245. doi: 10.1038/emm.2016.81.

[17]. Lemeshko, V.V. (2021). Electrical control of the cell energy metabolism at the level of mitochondrial outer membrane. Biochimica et Biophysica Acta (BBA) - Biomembranes,1863, 1, 183493. https://doi.org/10.1016/j.bbamem.2020.183493.

[18]. Bar-Peled, L., Kory, N. (2022). Principles and functions of metabolic compartmentalization. Nat Metab. 4(10):1232-1244. doi: 10.1038/s42255-022-00645-2.

[19]. Semenza, G.L. (2022). Breakthrough science: hypoxia inducible factors, oxygen sensing, and disorders of hematopoiesis. Blood.,139,16, 2441–2449. doi.org/10. 1182/blood. 2021011043.

[20]. Ullah, K., Wu, R. (2021). Hypoxia-Inducible Factor Regulates Endothelial Metabolism in Cardiovascular Disease. Front Physiol.;12:670653. doi: 10.3389/fphys.2021.670653.