Integrative concept of homeostasis: translating physiology into medicine

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Abstract

To truly understand living systems they must be viewed as a whole. In order to achieve this and to come to some law to which living systems obey, data obtained on cells, tissues and organs should be integrated. Because there are no such laws yet, there is usually a long path for physiological findings obtained by reductionist approaches to be translated into medical practice. The concept and accompanying equations of homeostasis presented here are aimed to develop biological laws and to bridge this gap between physiology and medicine. The concept of homeostasis takes into account energy input and output, enlisting all relevant contributors. In homeostasis, input should equal the output. What I suggest here is that if the system is out of homeostasis, the homeostasis may be regained by changing any of the input or output components in an adequate manner, not only the one that has changed first. Proposed equation should enable for the new lab findings regarding any pathophysiological conditions to find a more direct use in medicine. It should also ease 'decision making' in medicine and make therapy development and treatment outcome more straightforward and predictable. Finally, to recognize the basic laws of living systems enables for evolutionary adaptations and processes to be understood better.

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Introduction

It seems to be the right time for physiology and medicine to re-embrace the ancient all-embracing concept. As the knowledge of living systems accumulated, the phases of simplification rising hopes that physics and chemistry, medicine, molecular biology, and finally genetics will provide all the answers, was subsided by the despair and noise of the myriad of generally unorganized data without much of fundamental knowledge [1]. The first to note that reductionist sciences should be complemented by integrative approaches was Claude Bernard more than 100 years ago. The brilliant thinker was aware of the lack of data characteristic for those times and proposed that the most useful path is to seek new facts instead of premature attempts to reduce biosystems to equations [2,3]. Schrödinger noted in 1944 that the science is beginning to acquire reliable material for welding together all that is known into one whole [4]. Nowadays the situation is largely different as we have more facts than anyone could ever handle on its own, and there are explosions of new knowledge on a weekly basis. This seems to overwhelm a large part of scientific community which shows a tendency to trench in small specialized niches. However, as Schrödinger proposed, some of us should venture to embark on a synthesis of facts and theories in order to create some fundamental laws of physiology, even at the risk of making fools of ourselves. This paper represents my humble attempt toward an integrative concept in physiology. Looking upon a living system as a whole, I introduce some parameters that should enable differentiation between physiological and pathophysiological conditions, and laws that could make 'decision making' in medicine and treatment outcome more straightforward and predictable.

What is homeostasis?

Living beings are open thermodynamic systems, exchanging energy and matter with the exterior [5]. They also exchange "information", a term introduced by Von Bertalanffy to account for the functional role of nervous tissue and internal order of the system ("negative entropy") [6,7]. There is a continuous exchange of energy and matter between biological systems and their surroundings, so living systems achieve thermodynamic equilibrium only when they seize to exist as such (*i.e.* are dead). In the language of thermodynamics all processes in biological systems are irreversible, as the reversibility can only be attributed to the systems in the equilibrium. Schrödinger has noted that biological systems need to be in a nonequilibrium state because of intrinsic reasons [4]. The reasons are implied by Bernard's postulate that living organisms only exist in controlled liquid interior milieu [2,3]. Although never in equilibrium, living systems may acquire a steady state of nonequilibrium (X_S) which represents a stabile dynamic regime maintained away from thermodynamic equilibrium with the surroundings during which system maintains constant composition in spite of irreversible processes. Only several steady states have been described in mammals: quiet wakefulness, NREM sleep's phases three and four, and hibernation [8]. These states are used to describe an actual state of the system ($X(t)$) by the following equation: $X(t) = X_S + x(t)$, with $x(t)$ describing fluctuations (deviations form X_S independent of the environment) and perturbations (deviations from X_S provoked by the interference of the environment with intrinsic dynamics) from the average values of specific parameter (*e.g.* metabolic rate, heart rate, breathing rate, blood pressure, etc) [9]. This approach is very useful in describing various parameters of the functioning of biological system, during specific periods of time. However it does not enable discrimination between physiological and pathophysiological conditions, nor it takes into account interrelations between the parameters. For an example, heart rate can be increased by exercise but also by cocaine abuse, where the first condition is normal/physiological, while the later is abnormal/pathophysiological. It seems that an alternative approach is necessary in order to be able to describe and differentiate physiology from pathophysiology in humans.

From the teleological point of view, homeostasis represents a state characterized by balance and stability [10]. Balance is used to describe the relationship between the system and its surroundings (external balance), and the relationship between different internal processes in the same system (internal balance), in which the input equals the output [11]. The term stability is used to describe the tendency of the system to regain balance after deviation from previous state [8]. Stability implies mutual dependence of variables [12]. It can be global (actual state is near balance) or local (actual state if far away from balance) [9]. So, homeostasis can be defined as time- and initial-condition-independent globally stabile state of nonequilibrium of a living system in which the interactions of system with the surroundings and internal processes are overall in balance or very near it. We propose that a system is in homeostasis during any period of time if:

$$\boldsymbol{A_i + B_i + C_c + D_{ox} \approx A_o + B_o + C_a + D_r + E_o}$$

The components of equation defining homeostasis are:

A: Energy input (food, heat, mechanical energy (*e.g.* pressure), electromagnetic energy) – $\boldsymbol{A_i}$; and output (waste, work, heat and energy lost by evaporation, energy invested in the maintenance of volume and shape) – $\boldsymbol{A_o}$

$$\boldsymbol{A_i = E_f + Q_i + E_{mi} + E_{em}}$$

E_f – chemical energy contained in food; Q_i – thermal energy received from the environment; E_{mi} – mechanical energy (e.g. delivered by pressure); E_{em} – electromagnetic energy (received from the sources of electromagnetic irradiation).

$$\boldsymbol{A_o = E_w + A + Q_o + E_{mo} + E_t}$$

E_w – chemical energy of excreted compounds; A – work (physical work, work invested in preserving posture in gravitational field, internal organ contractions (heart, bowls)); Q_o – thermal energy dissipated into environment and invested in temperature maintenance; E_{mo} – energy invested in the maintenance of volume and shape; E_t – energy invested in the transport (renal function, active transport).

B: Informational (emotional, social, environmental) input ($\boldsymbol{B_i}$) i output ($\boldsymbol{B_o}$)

$$\boldsymbol{B_i = \sigma E_s + \varepsilon E_e}$$

E_s – energy invested by the individuals of the same or other species into various forms of communication (verbal, emotional) with the individual (system); σ *– utility coefficient; E_e – energy invested by the environment into creating specific living conditions;* ε *– coefficient of adaptation (this parameter takes into concern the ability of the individual to*

adapt, as well as the ability to change the environment, e.g. by building shelters, wearing clothes, etc).

$$B_o = E_c + E_r$$

E_c – *energy invested by the individual into communication with the individuals of the same or other species (e.g. humans interact with humans, but also with pets or even plants);* E_r – *energy invested into the neurological/endocrine response to social and emotional stimuli.*

Analogous to the concept presented here is the term "information", which was introduced by Von Bertalanffy to account for the functional role of nervous tissue in the regulation of the metabolism via endocrine and sympathetic/parasympathetic activity [6,7]. I have tried to quantify the information via energy that is invested in its generation, and utility coefficient evaluating the effects made on receiving individual. Parameters E_e and E_c integrate selected living being in the whole Earth system [13].

C: Catabolism (C_c) and anabolism (C_a)

$$C_c = E_{c+} - E_{c-}$$

E_{c+} – *energy released by the degradation of compounds;* E_{c-} – *energy invested in compound degradation.*

$$C_a = E_{a-} - E_{a+}$$

E_{a-} – *energy invested in compound synthesis;* E_{a+} – *energy released in the course of compound synthesis.*

Catabolism is presented on the input side using the logic that the drive of the surrounding is to decompose living system.

D: Oxidation ($\boldsymbol{D_{ox}}$) and reduction ($\boldsymbol{D_r}$)

$$\boldsymbol{D_{ox} = E_{ox-} - E_{ox+} + E_{rrox}}$$

E_{o-} – energy lost by the oxidation (e.g. energy that must be invested to repair damaged DNA); E_{o+} – energy spared by oxidation (e.g. oxidative degradation of neurotransmitters); E_{rro} – energy invested into refractory response against oxidants.

$$\boldsymbol{D_r = E_{r-} - E_{r+} + E_{rrr}}$$

E_{r-} – energy invested in reduction (e.g. GSSG → 2GSH); E_{r+} - energy spared by nonspecific reduction; E_{rrr} – energy invested into refractory response against reductants.

The oxidation is on the input side of the equation since most living systems live in oxygen atmosphere and use this oxidizing species for vital processes.

E: Entropy

$$\boldsymbol{E = E_o}$$

$\boldsymbol{E_o}$ – entropy produced inside the system as a result of irreversible processes.

The entropy relationship in living (open) systems was defined by Prigogine: $dS = dS_i + dS_e$, where dS (E_o in my equation) is the total entropy change in a system, dS_i is the internal entropy generated by the irreversible processes that take place in the system, and dS_e is the entropy change with the surroundings. For the system to maintain itself in a non-equilibrium steady state, dS_e must be equal to or larger than the entropy produced by internal processes. Therefore, production of entropy is intrinsic to living systems [14]. It should be stressed that my equation is in agreement with the minimum entropy production as a condition for maximum efficiency of living systems [15].

Out of homeostasis

When the system is in homeostasis, the energy shift from homeostasis (ΔH) equals or is next to zero:

$$\Delta H = (A_i + B_i + C_c + D_{ox}) - (A_o + B_o + C_a + D_r + E_o) \approx 0$$

If the system is pushed out of homeostasis ($\Delta H \neq 0$), it becomes unstable (or locally stabile [9]). From a thermodynamic point of view, unstable system is energetically unfavorable, so it is pointed towards lower energy, more stabile states by dissipation. From the physiological point of view, the system tries to regain homeostasis by changing the values of components in the equation. Intrinsic stability draws the system back to homeostasis, although final values of particular parameters may be altered in comparison to starting values (adaptation). Parameters that define functioning of living systems are interrelated, so when the system is out of balance, it is not important for them to regain their previous values (specific attracting points [14]), but to be modified in a fashion that has a balance of the system as a result. In line with this, I propose that $\Delta H = 0$ represents the main attracting point of living systems, with a limitation that each parameter has a specific range of allowed values (fractal attractors [14]). A key command centre of stability which aims to minimum entropy and maximum efficiency of the system seems to be parasympathetic nervous system, which favors constancy and stability of internal variables and environment [8]. Time that is required for regaining the homeostasis (the time is of crucial importance in medicine), depends on energy shift from homeostasis (ΔH) and system's ability to adapt (α – adjustment coefficient [J/s]):

$$t_H = \Delta H/\alpha$$

Adjustment coefficient (α) varies widely, taking into account the nature of stimulus that shifted the system from homeostasis. For an example A_i and therefore ΔH could be extremely increased by high acute food uptake. However, the system is well adapted to such situation, so α is high and consequently t_H is short. It is a question of efficiency for a living system to be organized and commanded in a fashion to be prepared for any fluctuation or perturbation that can be expected to occur. Living systems are able to 'learn' what to expect, and they can increase the adjustment coefficient for specific fluctuation or perturbation. For an example, when a living system first meets specific pathogen, α is low and t_H is long, but due to the plasticity of immune system, next encounter should be much shorter. However, some things are hard to learn. *E.g.* living systems can adapt to some extent to radiation [17], or even turn the effects of radiation into their own benefit (process known as hormesis), but the value of α in this case is generally very low. So in a misfortune setup a few quanta of gamma-irradiation, which provoke modest changes of ΔH, could lead to a set of mutations and to the formation of malignant cells, so t_H could be very long.

The value of the adjustment coefficient and energy shift separates physiological conditions (high α and/or low ΔH) from pathophysiological ones (low α and/or high ΔH). As α and ΔH are interrelated by t_H, physiological setup could be defined as the state in which the system is in the homeostasis ($t_H = 0$) or the state in which the system can regain homeostasis in sufficiently short period of time (*e.g.* for humans t_H should be up to one day or so). Medical treatment can increase α and shorten t_H. According to the presented theory, any pathophysiological condition is curable if the treatment could be conducted long enough. It should be stressed that if different systems are to be compared (*e.g.* humans and laboratory animals used as models), t_H and α should not be considered in the terms of absolute times, but rather in the terms of what Andresen defined as eigen time intrinsic to the system and dependent on the interior processes [15]. In relation to this, adjustment coefficient is principally dependent of the body mass of specific living system. Higher body masses stand for higher values of α. This is in agreement with Schrödinger's concept that large systems are better operated and controlled and less affected by surroundings, than small [4].

Testing the hypothesis: aging, obesity, cancer, neurodegeneration, and death

Presented equation is in agreement with the theory of aging. Aging could be defined as a process during which adjustment coefficients generally decrease. Aging is known to be related to pronounced oxidation [17], and decreased capacity to degrade energy and produce entropy [18]. In the terms used here D_{ox} is increased, while C_a and E_o are decreased, leading to $\Delta H > 0$. One intervention that has been documented to slow down the aging process is caloric restriction [19], which is an equivalent of the decrease of A_i. There are other components of my equation that could be modulated for fine tuning of homeostasis disturbed in the aging process. A moderate physical activity, which has dual homeostasis-promoting effects by increasing both A_o and E_o [20], seems to provoke anti-aging effects [21]. A decrease in emotional input (B_i) in elders seems to represent an adaptation directed towards the maintenance of homeostasis. *E.g.* Williams and co-authors have shown that the control over emotional functions increase with age [22]. In other words, utility coefficient, σ is decreasing in the course of aging, resulting in the decrease of B_i.

There is a very interesting contemporary example, related to high food uptake, which shows correctness of my concept of homeostasis. Two seemingly contradictory trends are present in modern Western society. On the one side, the number of obese people is increasing, related at least partially to excessive uptake of fructose-rich syrup [23], and on the other side is a trend of longer life span. Olshansky and co-workers have reported in 2005 that because of obesity, youth of today will have shorter lives than their parents [24]. However, this has opened a public debate in which some authors like J. Vaupel, director of Max Planck Institute for Demographic Research, have noted that there are not strong evidences that obesity decreases life expectancy. In addition, Olshansky himself has reported recently that the life expectancy in America is in fact increasing, in spite of rising number of obese people [25]. The explanation for such ambiguity may lay in high antioxidative capacity of fructose and its metabolic derivatives [26]. Fructose which takes important role in modern obesity [23], could balance high energy input by decreasing oxidation. In parameters used here, high A_i is balanced by low D_{ox} making ΔH less pronounced than expected. This seems to lead to a paradox of simultaneity of obesity and homeostasis.

Cancer is characterized by uncontrolled anabolism of specific tissue(s). As C_a is increased ($\Delta H < 0$), the treatment should modify other parameters in order to provide system with a homeostasis. First, energy input (A_i) should be increased, in order to prevent for the metabolism of other tissues to suffer from the lack of energy, but to such a degree not to provoke a significant increase of entropy production (E_o). Secondly, the oxidation (D_{ox}) should be increased. Promoted oxidation is *modus operandi* of cancer treatment with radiation therapy and some chemotherapeutic agents [27,28]. In addition, Chen and co-workers have shown recently that ascorbate acting as prooxidant can selectively kill cancer cells via oxidative damage [29]. Finally, chemotherapy can lower C_a, thus decreasing time necessary for pushing back the system into the homeostasis.

In contrast to cancer, neurodegenerative conditions are related to increased catabolism (C_c) of nervous tissue. So according to the presented hypothesis, for the system to cope with the loss of homeostasis ($\Delta H > 0$), energy input (A_i) and oxidation (D_{ox}) should be decreased, while energy output (A_o), emotional output (B_o) and reduction (D_r) should be increased. Amazingly, these are exactly the points addressed by the currently available approaches for the treatment of neurodegenerative conditions, which are based on caloric restriction (decreased A_i), antioxidant/reducing agents supplementation (decreased D_{ox}, increased D_r), exercise (increased A_o), and intellectual activity (increased B_o), each of which is showing neuroprotective effects [30-33].

Death is the final state of homeostasis ($\Delta H = 0$), in which the production of entropy is balanced by oxidation, catabolism and electromagnetic input, while all the other parameters equal zero. It emerges when the system is pushed far away from homeostasis ($\Delta H > \Delta H^D$) or is not adapted to the specific change ($\alpha < \alpha^D$) (superscript ^{D} stands for death), so that it could not regain homeostasis in no other way but to die. It seems that death represents a victory of balance and stability over interior milieu. When one says that adaptive self-organization occurs by the means of a complexication of structure, I try to translate, in ordinary language, the physical and statistic fact that the system becomes thermodynamically 'improbable' and hence, structurally instable, so, prone to physical disorganization. According to H. Simon, the father of Artificial Intelligence, any failure in the organization will not destroy the system as a whole but only decompose it to the next stabile subsystem assembly [34]. Death occurs when it is the only next stabile assembly of the system.

Conclusion

To translate physiological findings on any pathophysiological condition into clinical practice is a long and formidable task. This fact can be mostly attributed to the risks of failure or unwanted effects and seemingly unpredictable outcome. The presented concept (and equation) of homeostasis could make this process much easier and straightforward. If fundamental principles are take into account, as I have tried to do, we would be able direct medical research and to predict the outcome of any step taken in the treatment of human pathophysiologies. Even more, integrative concept of homeostasis of system (human organism) as a whole, may explain some “paradoxes” in medicine, which could not be understood by reductionist knowledge. I would like to emphasize that presented concept is in its conception and therefore represents a subject of criticism and further development.

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