OPINION ARTICLE

Integrative concept of homeostasis: translating physiology into medicine [version 1; peer review: peer review discontinued]

Ivan Spasojević

Department of Life Sciences, Institute for Multidisciplinary Research, University of Belgrade, Belgrade, Serbia

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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 that living systems comply with, the reductionist approach, which has delivered a tremendous amount of data so far, should be complemented with integrative concepts. The current paper represents my humble attempt towards an integrative concept of homeostasis that would describe the (patho)physiological setup of adult human/mammal system, and that might be applicable in medicine. Homeostasis can be defined as time- and initial-condition-independent globally stable state of non-equilibrium of a living system in which the interactions of system with the surroundings and internal processes are overall in balance or very near it. The presence of homeostasis or the shift from homeostasis of an adult human/mammal system can be described by equation that takes into account energy and informational input and output, catabolism and anabolism, oxidation and reduction, and entropy, where changes in the input should equal changes in the output within a specific period of time. Catabolism and oxidation are presented on the input side since the drive of the surroundings is to decompose and oxidize living systems, *i.e.* systems are under constant 'catabolic and oxidative pressure'. According to the equation, homeostasis might be regained by changing any of the input or output components in a proper manner (and within certain limits), not only the one(s) that has/have been changed in the first place resulting in the deviation from homeostasis.

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Corresponding author: Ivan Spasojević (redoxsci@gmail.com)

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Introduction

It seems to be the right time for physiology and medicine to embrace the ancient all-embracing concept. As information on living systems accumulated, the phases of simplification raising hopes for physics and chemistry, medicine, molecular biology, and finally genetics to provide all the answers and deliver laws that fully depict interconnected functions of living systems, were subsided by disappointment and noise of myriad of (sometimes contradicting) data without much fundamental knowledge¹. Over a 100 years ago, the first to note that reductionist sciences should be complemented by integrative approaches was Claude Bernard. 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 whole⁴. Nowadays the situation is largely different as we have more facts than anyone could ever handle on his own, and there are explosions of new knowledge on a monthly basis. Therefore, 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. So far, only few laws have been developed, such as Kleiber's law (relation between metabolic rate and mass) and the power-law (organization of metabolic networks at the level of the organism)^{5,6}. In addition, there is a complex dynamic energy budget theory with related models which strives to describe heterotrophic unicellular organisms, animals, and related structured populations in terms of energy assimilation and utilization as a function of the state of the organism and of its environment, and takes into account the stoichiometry of organisms, various metabolic processes (feeding, growth, reproduction, maturation and maintenance), and life stages (embryo, juvenile and adult)⁷. The current paper represents my attempt towards a simple integrative concept that would describe the physiological setup of adult human/mammal system and that might find application in medicine.

What is homeostasis?

Living beings are open thermodynamic systems, exchanging energy and matter with the exterior⁸. 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")^{9,10}. There is a continuous exchange of energy and matter between biological systems and their surroundings, so living systems achieve thermodynamic equilibrium only when they cease 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 non-equilibrium state because of intrinsic reasons⁴. 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 non-equilibrium (X_s) that represents a stable dynamic regime maintained away from thermodynamic equilibrium with the surroundings during which system maintains constant composition in spite of irreversible processes. So far only a few steady states have been described in mammals: quiet wakefulness, NREM sleep's phases three and four, and hibernation¹¹. These states are applied to describe an actual state of the system ($X(t)$) by the following equation: $X(t) = X_s + x(t)$, with $x(t)$

standing for fluctuations (deviations from 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, glucose blood level, blood pressure, etc)¹². This approach is very useful in describing various parameters during specific periods of time. However it does not take into account interrelations between the parameters and does not discriminate physiological from pathophysiological settings on the level of the whole system.

From the teleological point of view, homeostasis represents a state characterized by balance and stability¹³. Balance describes the relationship between the system and its surroundings (external balance), and the relationship between different internal processes within the system (internal balance), in which input equals output¹⁴. The term stability describes the tendency of the system to regain balance after deviation from previous state⁸. Stability implies mutual dependence of variables¹⁵. It can be global (actual state is near balance) or local (actual state is far away from balance)¹². Therefore, homeostasis can be defined as time- and initial-condition-independent globally stable state of non-equilibrium of a living system in which the interactions of system with the surroundings and internal processes are overall in balance or very near it. I propose that if an adult human/mammal system (period of growth is over, stores of energy in the form of electric potential of cells, fat depots and liver glycogen are made, but the period of aging has not started yet) is in homeostasis, it will maintain homeostasis as long as changes in total energy input equal (or are very near) changes in total energy output:

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

The components of equation defining homeostasis are:

A_i – Energy input: the sum of chemical energy contained in food, and thermal and electromagnetic energy received from the environment.

A_o – Energy output: the sum of chemical energy of excreted compounds, work (physical work, work invested in preserving posture in gravitational field, internal organ contractions), thermal energy dissipated into environment, heat lost due to evaporation, energy invested in the maintenance of volume and shape, energy invested in the transport (renal function, active transport).

B_i – Informational input: The sum of energy spared via learning from other systems (*e.g.* information obtained from other members of the species can increase individual's ability to adapt) and energy spared via spontaneous responses to environmental challenges (this parameter takes into account the ability to change the environment, *e.g.* by wearing clothes, taking shelter).

B_o – Informational output: The sum of energy invested by the individual into communication with the surroundings (*e.g.* other members of the species), and energy invested into the neurological/endocrine response to exogenous stimuli. Of note, B_i and B_o are essentially different parameters. The first reflects indirect energy benefits and integrates a living being in the whole Earth system¹⁶. B_o describes the loss of energy via social feedback (*e.g.* speech-related mental activity) and via processing of received data (social, emotional, environmental) and pertinent responses of the nervous

and endocrine system. Analogous to B_o is the term “information”, which has been 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^{9,10}.

C_c – Catabolism: The difference between energy released by the degradation of cell and tissue components/compounds (proteins, lipids, DNA, etc) and energy invested in degradation of compounds. Catabolism is presented on the input side because the drive of the surrounding is to decompose living system, *i.e.* ‘catabolic pressure’ is imposed from the outside. In addition, compounds that are catabolized represent components of reserve and structure (terms coined by Kooijman⁷), which are ‘interstations’ of input energy (this does not mean that they are metabolically inert). *I.e.* energy from food is stored in reserve and structure and can be extracted from reserve and to some level from structure for the purpose of homeostasis maintenance.

C_a – Anabolism: The difference between energy invested in compound synthesis and repair and energy released in the course of compound synthesis.

D_{ox} – Energy released via oxidation. The oxidation is on the input side of the equation since mammals live in oxygen atmosphere *i.e.* they are exposed to ‘oxidative pressure’. In addition, mammals introduce oxygen into vital processes, which further supports the logic that oxidation should be on the input side of equation.

D_r – Reduction: The sum of energy invested in reduction (*e.g.* $GSSG \rightarrow 2GSH$) and energy invested in refractory response against exogenous reducing agents. Living systems have to invest energy in reduction to fight exogenously imposed oxidation.

E_o – Entropy produced inside the system as a result of irreversible processes. Production of entropy is intrinsic to living systems. The entropy relationship in living (open) systems has been defined by Prigogine: $dS = dS_i + dS_e$, where dS (ΔE_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 processes¹⁷. It should be stressed that presented equation for homeostasis is in agreement with the minimum entropy production as a condition for maximum efficiency of living systems¹⁸.

An additional prerequisite for homeostasis maintenance that cannot be expressed in the terms of energy is that the system should not be deficient in essential nutrients (*e.g.* microelements, essential amino acids) and water.

The presented equation of homeostasis is (at least at the moment) largely descriptive, as the majority of input and output parameters are hard to measure/estimate and express in units. So, what can be gained by an approach that appears to be a step in the opposite direction to simplifying and making homeostasis a measurable variable or parameter? The potential gain here lays in applications in medicine

via enabling discrimination between physiological and pathophysiological conditions, aiding the development of general therapeutic strategies, and providing explanations for some medical “paradoxes”, all of which require the perspective of human system as a whole.

Out of homeostasis

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

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

If the system is pushed out of homeostasis ($H \neq 0$), it becomes unstable (or locally stabile¹³). From a thermodynamic point of view, unstable system is energetically unfavorable, so it is pointed towards more stabile lower-energy states via 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 might be altered in comparison to starting values. Parameters that define homeostasis are interrelated, so when the system is out of balance, it is not important for deviated parameters to regain their previous values (specific attracting points¹⁷). Instead, those and/or other parameters should be modified in a fashion that has a balance of the whole system as a result, with a limitation that each parameter has a specific range of allowed values (fractal attractors¹⁷). To put it simply, the change of one parameter and pertinent loss of homeostasis can be compensated by an appropriate change of another parameter. In line with this, $H = 0$ represents the main attracting point of adult human/mammal systems. Key command centre of stability which aims to minimum entropy and maximum efficiency of the system appears to be parasympathetic nervous system. It favors constancy and stability of internal variables and environment¹¹. The time required for regaining the homeostasis depends on energy shift from homeostasis and system’s ability to adjust (α – adjustment coefficient [J/s]):

$$t_H = |H|/\alpha$$

Adjustment coefficients vary widely depending on the nature of stimulus that shifted the system from homeostasis. It is a question of efficiency for a living system to be organized and commanded in a fashion that allows timely response to any fluctuation or perturbation that can be expected to occur. For an example, A_i and therefore H could be extremely increased by high acute food intake. However, the system is well adapted to such situation, so α is high and consequently t_H is short. In addition, living systems are able to ‘learn’ what to expect, and they can increase the adjustment coefficient for specific fluctuation or perturbation. *E.g.* when a living system first meets specific pathogen, α is low and t_H is long, but the next encounter might be much shorter due to the plasticity of immune system¹⁹. However, some things are hard to learn. Living systems can adapt to some extent to radiation²⁰, or even turn the effects of radiation into their own benefit (process known as hormesis)²¹, but the value of α in this case is generally very low.

The value of the adjustment coefficient and energy shift separates physiological conditions (high α and/or small $|H|$) from

pathophysiological ones (low α and/or large $|H|$). Physiological setup could be defined as the state in which the system is in the homeostasis ($t_H = 0$) or homeostasis can be regained in sufficiently short period of time (for humans this time might be up to one day or so). Medical treatment can increase α and shorten t_H . It appears that any pathophysiological condition might be 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 time, but rather in the terms of what Andresen *et al.* defined as eigen time intrinsic to the system and dependent on the interior processes¹⁸. 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 , in agreement with Schrödinger's concept that large systems are better operated and controlled and less affected by surroundings compared to small systems⁴.

Examining the hypothesis: caloric restriction, obesity, cancer, neurodegeneration, aging, and death

Caloric restriction implies decreased energy input (A_i), and has been also proposed to result in increased entropy (E_o)²². Hence, in this case $H < 0$. This can be compensated via increased informational input (for example via usage of insulation to decrease heat loss), catabolism (degradation of compounds from reserve (fat) and structure (e.g. muscle loss²³)), and oxidation. Pertinent to the latter, it has been shown that caloric restriction leads to pronounced production of reactive oxygen species in mitochondria, which represents a beneficial adaptation according to the negative effects of application of reducing agents, under such settings, on life span²³. Clearly, output side of equation should be decreased in order to balance for caloric restriction-related decrease of energy input. For example, a decrease in the body core temperature (resulting in a decrease of heat loss, and hence lower A_o) is a known adaptation to caloric restriction²⁴.

There is a very interesting contemporary paradox related to high food intake, which might be explained by the concept of homeostasis. A recent large meta-analysis study has shown that the inflection point of the body-mass-index–mortality curve is placed in the overweight range²⁶. In addition, the expected life span is increasing in Western society in spite of the overweight epidemic²⁷. Much of the ongoing problem can be ascribed to excessive consumption of fructose-rich syrup²⁸. In relation to this, the explanation for so-called “obesity-mortality paradox” might be found in antioxidative and metabolic properties of fructose. Fructose and its metabolic derivatives show high antioxidative capacities²⁹, and more importantly fructose promotes the production of reducing agent NADPH under pro-oxidative conditions. In brief, fructose induces the expression of fructose 1,6-bisphosphatase that up-regulates glycolysis³⁰. Under pro-oxidative settings, hydrogen peroxide inhibits glyceraldehyde 3-phosphate dehydrogenase³¹. This results in the accumulation of glyceraldehyde 3-phosphate which is pushed towards NADPH-producing pentose phosphate pathway. Hence, in fructose-rich diet, high energy input (A_i) might be balanced by decreased oxidation (D_{ox}) and/or increased reduction (D_r), resulting in simultaneity of overweight and homeostasis. Finally, fructose appears to affect brain activity in a different manner compared to glucose³², so it is tempting to speculate that fructose (sweet taste) might increase informational output (B_o).

Cancer is characterized by uncontrolled anabolism (C_a is increased i.e., $H < 0$) of specific tissues³³. According to the homeostasis equation, treatment should involve increased energy input (high calorie diet), in order to prevent for the metabolism of healthy tissues to suffer from the lack of energy. Secondly, D_{ox} should be increased. Pertinent to this, promoted oxidation is *modus operandi* of cancer treatment with radiation therapy and some chemotherapeutic agents^{34,35}. Finally, chemotherapy directly targets C_a .

In contrast to cancer, neurodegenerative conditions are related to increased catabolism (C_c) of nervous tissue³⁶. For the system to cope with the loss of homeostasis ($H > 0$), 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. 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 are showing neuroprotective effects^{37–40}. In addition, according to the equation, entropy production should be increased in neurodegeneration in order to regain homeostasis. This can be achieved by exercise⁴¹, and caloric restriction²².

Aging could be defined as a process during which adjustment coefficients generally decrease. Aging is known to be related to pronounced oxidation²⁰, and decreased capacity to degrade energy and produce entropy⁴². In the terms used here, D_{ox} is increased, whereas C_a and E_o are decreased, resulting in $H > 0$. One intervention that has been documented to slow down the aging process is caloric restriction (decrease of A_i)⁴³. In addition, a moderate physical activity, which has dual homeostasis-promoting effects by increasing both A_o and E_o ⁴¹, seems to provoke anti-aging effects⁴⁴. Finally, an increase in the informational output (B_o) via social interactions might be also beneficial in slowing down the aging process⁴⁵.

Death is the final state of homeostasis ($H = 0$). It emerges when the system is pushed far away from homeostasis ($|H| > |H^p|$) or is not adapted to specific change ($\alpha < \alpha^p$), so that it cannot regain homeostasis in no other way but to die. It seems that death represents a victory of balance and stability over interior milieu. Adaptive self-organization occurs by the means of a complexification of structure. So when the system becomes thermodynamically ‘improbable’ and hence structurally instable, it is 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 assembly⁴⁶. Death occurs when it is the only next stabile assembly of the system.

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