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Views & Comments

The Entropy Perspective on Human Illness and Aging

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1. Entropy and its implications in human disease and aging

Entropy, which is a thermodynamic property or an interpretation of the second law of thermodynamics, was first defined in 1865 by the German physicist Rudolph Clausius [1]. It eventually evolved into a general scientific concept that is of universal and paramount importance in three aspects. First, entropy is a measurable physical property that is commonly associated with a state of chaos, disorderliness, randomness, or uncertainty of any systems [2]. Second, entropy is a measure of the amount of energy that is unavailable to do work [2]. Third, the universe or an isolated system always obeys "the principle of entropy increase" that irreversible or spontaneous processes can occur only in the direction of entropy increase—that is, the direction of increasing chaos, disorder, randomness, or uncertainty [2].

When applied to living systems, a state of disorderliness implies the deterioration of physical structures—for example, the misfolding or deformation of macromolecules such as proteins, DNA, and RNA, or the disruption of tissues and organs [3–5]. "Loss of the capability to work" with entropy generation means the decline or loss of the physiological functions of molecules, cells, tissues, or organs. Living systems have the capability to reverse the principle of entropy increase within a certain period during development (e.g., during the early phase of development and growing) and under certain conditions (i.e., given sufficient nutrient intake, efficient metabolic activities, strong self-defense and self-healing capabilities, etc.). This is because, as an open system with a highly ordered dissipative structure that is far from equilibrium, an organism can exchange matter, energy, and information with its surrounding environment to acquire "negative entropy" (i.e., decreased disorder) to counter entropy increase; meanwhile, it can shed the entropy generated in its body out into the environment [5].

An increasing body of scientific evidence indicates that entropy increase lies at the root of the deterioration of human health and acceleration of the human aging process [6,7]. Silva and Annamalai [7] found that the entropy generated over the lifespan of an average individual (ending with natural death) is around 11 404 $kJ \cdot K^{-1} \cdot kg^{-1}$ of body mass, and that this "maximum lifespan entropy" predicts a lifespan of 73.78 and 81.61 years for the average US male and female individuals, respectively, which correspond closely to their statistical average lifespans of 74.63 and 80.36 years. The findings of this study support the theory that the entropy generation rate (EGR) determines the rate of aging: The higher an EGR a person has, the faster that person approaches the maximum lifespan entropy over a lifetime and the shorter that person's lifespan [7,8].

The difference between "life" and "death" is nothing more than the difference between the orderliness and disorderliness of living systems. "Life" is maintained by a high degree of orderliness, or a low-entropy state in the body, while "death" is the result of the gradual loss of the ability to maintain a low-entropy state. By the same token, "health" means that the body is in a highly ordered low-entropy state, whereas "disease" implies that the structures and functions of an organism fall into disordered or high-entropy states. In other words, an increase in entropy—that is, a loss of orderliness or an increase in the disorderliness of the function and architecture at the molecular, cellular, tissue, organ, or system levels—is deemed to cause disease.

Scientific research has demonstrated that, in a disease state, the entropy of the body increases, which is manifested in—but not restricted to—the diseased tissue or organ. The mechanistic link between entropy generation and pathogenesis has been confirmed in metabolic diseases (simple obesity, diabetes, metabolic hypertension, cancer, gout, osteoporosis, etc.), metabolic syndrome (insulin resistance, obesity, hyperglycemia, hypertension, dyslipidemia, hyperuricemia, hyperviscosity syndrome, fatty liver disease, etc.), metabolic inflammation, viral and bacterial infections, chronic obstructive pneumonia disease, Alzheimer's disease, and various heart diseases (coronary heart disease, heart failure, arrhythmia, etc.) [6,7,9–25]. It is noteworthy that entropy increase occurs in patients with various cancers, including lung, stomach, bowel, breast, ovarian, and prostate cancers, along with hepatocellular carcinoma and melanoma [9–14]. Moreover, these conditions can all be ascribed to the loss of orderliness at the cellular, subcellular, proteomic, transcriptomic, and genomic levels. In addition, immune entropy has been used to measure the integrity and function of the immune system and its relationship with the health of the population, and virus-infected or breast cancer patients have been found to have greater immune entropy generation than healthy people.

While entropy increase has been well recognized as the root of disease, a question remained unanswered: How does the human body maintain its low-entropy state?

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2. Potential mechanisms for maintaining the body's low-entropy state

Humans are born with innate self-organizing, self-defense, self-healing, and anti-wear-and-tear capabilities. Herein, I propose that these four attributes form the core mechanism for preserving the low-entropy state of the human body. The evidence for this hypothesis is presented in the following subsections.

2.1. The self-organizing system

Self-organization refers to the ability of the subsystems or components in an open system to spontaneously—often seemingly purposefully—form certain highly organized complex and integrative spatial, temporal, and spatiotemporal physiological architectures with associated functions (i.e., an organism's morphogenesis) according to genetic blueprints or programs without external instructions [26–29]. This is a fundamental characteristic of living systems. At the cellular level, cells inherently possess the ability to self-organize into the tissues and organs that comprise the whole body, and the anisotropies displayed by cells are evident in the dynamic processes that constitute life, including cell development, movement, and division [27–31]. At the genomic level, it has been stated by Misteli [32] that genomes have complex three-dimensional (3D) architectures that are largely driven by function, and that the structural features of chromatin act as modulators, rather than as binary determinants, of genome activity. The interplay of these principles in the context of self-organization accounts for the emergence of structural chromatin features and the diversity and single-cell heterogeneity of nuclear architecture in cell types and tissues. It also explains the evolutionarily conserved functional features of genomes [32,33]. One of the best-characterized examples of protein self-organization is represented by the oscillations of the Min proteins in *Escherichia coli*, which can help in sensing the geometry of the cell [34,35].

From the macroscopic view, highly organized, complex, and integrative spatiotemporal physiological architectures are well exemplified by the cardiac conduction system. The heart can be divided into several anatomical regions, according to their distinct structural and functional properties, including the sinoatrial (SA) node, atria (left atrium and right atrium), atrioventricular (AV) node, ventricles (left ventricle and right ventricle), valves, bundle of His, bundle branches, and Purkinje fibers [36]. These orderly spatialized inhomogeneous structures coordinate to generate sequential electrical excitation and mechanical contraction in order to supply blood all over the body. More specifically, the spatiotemporal sequence of electrical events during one full contraction of the heart muscle contains the following five main steps: ① An excitation signal (an action potential) is created by the SA node that contains pacemaker cells. ② The wave of excitation spreads across the atria, causing them to contract. ③ Upon reaching the AV node, the signal is delayed. ④ The excitation is then conducted into the bundle of His, down the interventricular septum. ⑤ The bundle of His and the Purkinje fibers spread the wave impulses along the ventricles, causing them to contract. If any of these spatiotemporally sequential events is disturbed and the physiological orderliness is lost, arrhythmia can occur, resulting in a chaotic contraction and leading to impaired cardiac function and blood supply.

Simply put, self-organization involves building or rebuilding orderliness from disorderliness in order to achieve a low-entropy state in a system. Its strength depends on the ability of the system to exchange matter, energy, and information with the surrounding environment—that is, metabolism. The stronger the body's self-organization is, the stronger its capability is to retain a low-entropy state and the stronger its power is to maintain a healthy state and vitality.

Self-organization relies on metabolic homeostasis—with the amount of nutrients being taken in matching the energy required to carry out life's physiological activities and to excrete wastes and discharge entropy (in the form of heat) to the environment—as metabolism mediates and governs the flow of matter and energy through the biosphere [37–39]. Metabolism is composed of two interdependent processes: catabolism and anabolism [40]. Catabolism is a series of processes of food digestion, nutrient absorption and transport, and the breakdown of large, complex molecules into smaller, simple ones accompanied by free energy production. It is an entropy-generating process in which nutrients are converted from high-orderliness structures into low-orderliness ones. It is also a process that prevents or eliminates the accumulation of waste products and entropy (in the form of heat production). Anabolism centers around growth and building—that is, it involves the organization of molecules, in which small, simple molecules (amino acids, nucleosides, fatty acids, and glucose) produced by catabolism are built up into more complex macromolecules (e.g., proteins, nucleic acids, lipids, glycogens, etc.). It is an entropy-discharging process that forms or preserves physiological structures with a high level of orderliness. Clearly, proper metabolism is the foundation of self-organization, and the maintenance of health involves a synchronized network of catabolic and anabolic signals in cells, tissues, and organs, which critically determines the level of entropy [37–39].

Based on this concept, I propose that the respiratory, digestive, cardiovascular, and excretory systems are the key to metabolism and thus to self-organization. While the respiratory and digestive systems are responsible for the intake of oxygen, water, and food, which are subsequently converted into "negative entropy" in the body, they also work with the excretory system to discharge the wastes and entropy generated during metabolism. The cardiovascular system is the hub for all metabolic activities. For convenience, here I amalgamate these systems into one and refer to it as the "metabolic/self-organizing system." This system is what makes the human body an open system with both an input port or entrance and an output port or exit, capable of exchanging matter, energy, and information with the outside world.

The physiological characteristics and functional importance of the metabolic/self-organizing system indicate that it is the system most prone to pathogenesis in the human body—particularly to infectious and chronic diseases. Statistics show that deaths caused by chronic noncommunicable diseases account for 85% of all deaths in China, of which cerebrovascular events, malignant tumors, respiratory disease, and heart disease rank as the top four causes of death. Lung cancer is the top-ranked cancer in both incidence and death rate, and chronic obstructive pneumonia is the most common chronic disease of the respiratory system. The top two to five malignant tumors (liver, stomach, esophageal, and colorectal cancers), as well as obesity and diabetes of the metabolic syndrome caused by an imbalance of intestinal flora, primarily originate from the digestive system. Cardiovascular and cerebrovascular diseases are common chronic diseases that seriously threaten lives with high morbidity, disability, and mortality rates. The number of people who die from cardiovascular (coronary artery disease, cardiomyopathies, heart failure) and cerebrovascular (stroke) diseases globally each year is as high as 15 million.

2.2. The self-defense system

As an open system, the human body ingests the elements of life from external sources to generate "negative entropy," thereby countering entropy increase and maintaining its low-entropy state. But the external environment is not merely the source of life for

organisms; it is also a source of disease and contains various pathogens (biological factors such as bacteria, viruses, fungi, and parasites) and other pathogenic factors (chemical and physical factors). When ingesting nutrients, it is inevitable for pathogenic factors to enter the body. By the same token, the body's metabolism, which generates free energy and the substances required for maintaining various structures, is always accompanied by the production of highly active free radicals (especially reactive oxygen species (ROS)) and other harmful metabolites, along with numerous and frequent errors in DNA replication, epigenetic alterations, incorrect transcription and splicing, errors in biochemical synthesis, and so forth. To safeguard against the invasion of exogenous pathogenic factors and the production of endogenous damaging metabolites, the human body is armed by nature with at least six defending mechanisms: immunity, the inflammatory response, endogenous antioxidants, the stress response, autophagy, and apoptosis. Here, I collectively refer to these six mechanisms as "the natural self-defense system." Self-defense is a countermeasure that involves protecting one's life and well-being from harm or danger; within the body, cellular self-defense synergizes with the whole-body protection provided by traditional immunity to confer pathogen resistance [40].

The immune system protects the human body by maintaining continuous surveillance over the whole body, fighting against the invasion of foreign pathogens, and eliminating internally generated deteriorating factors. Cell-autonomous immunity guards both individual immune and non-immune cells against the immediate threat of infection [40]. In this way, it maintains the orderliness, complexity, and integrity of the structures and functions of tissues and organs within the body. However, an overactive immune response can cause many autoimmune diseases, such as type 1 diabetes mellitus. A study has reported a global measure using Shannon's entropy to determine the immunosignatures of a diverse set of 800 people and in five individuals over a period of three months [41]. The authors of this study found that immune entropy is affected by certain population characteristics and varies widely across individuals. People with infections or breast cancer generally have higher entropy values than non-diseased individuals. The researchers accordingly advocated the use of immune entropy as a simple method to monitor health in individuals and populations. Furthermore, the analysis of entropy was used to evaluate immunogenetic parameters associated with immune-mediated disease [42]. Entropy has also been proposed to be a powerful indicator of the humoral immune response [43]. It is known that human immunodeficiency virus type 1 (HIV-1) accumulates mutations in and around reactive epitopes to escape recognition and killing by $CD8^+$ T cells. It has been revealed that this escape can be slowed significantly by lowering the entropy [44].

Under normal circumstances, inflammation is a defensive response of the body to harmful stimuli and a healing mechanism for injured tissues [45,46]. However, aggressive inflammation such as cytokine storm can induce life-threatening systemic inflammatory syndromes; likewise, chronic inflammation—also known as persistent, low-grade inflammation—is detrimental because proinflammatory factors can attack the body's own cells and tissues, leading to a wide range of chronic diseases (e.g., metabolic syndrome, which includes type 2 diabetes, heart disease, and obesity) [45,46].

ROS, which are produced by living organisms as a result of normal cellular metabolism and environmental factors, are a group of highly reactive ions and molecules that are powerful signaling mediators at physiological levels and are involved in the regulation of a variety of biological processes [47,48]. Physiological levels of ROS engage in metabolic regulation and stress responses to support cellular adaptation to a changing environment and stress. Increased ROS level in cancer cells may provide a unique opportunity to eliminate cancer cells via activating various ROS-induced cell death pathways or inhibiting cancer cell resistance to chemotherapy. However, excessive ROS can damage cell structures and alter their functions, establishing a state of high-entropy disorderliness: a situation known as "oxidative stress" [47,48]. Aerobic organisms have an integrated endogenous antioxidative system, which includes enzymatic and nonenzymatic antioxidants that are normally effective in scavenging ROS. However, under pathological conditions, the antioxidative system can be overwhelmed by excessive ROS.

The stress or "fight or flight" response is the emergency reaction system or the stress system of the body, and involves physiological and psychological mobilization in response to an individual's perception of various unexpected challenging or threatening situations [49,50]. The adaptive stress response depends upon a complex and highly interconnected neuroendocrine, metabolism, and cellular and molecular infrastructure. Dysregulation of the stress system (hyper- or hypo-activation) in association with potent and/or chronic stress can markedly disrupt the body homeostasis, leading to a state of cacostasis or allostasis, with adverse effects on many vital physiologic functions and a spectrum of clinical manifestations.

Autophagy, the natural, regulated quality-control mechanism of the cell that removes unnecessary or dysfunctional molecules or organelles, allows the orderly degradation and recycling of cellular components [51,52]. It has been recognized as a crucial defense mechanism against malignancy, infection, and neurodegenerative diseases and as an adaptive response to stress that promotes the survival of the cell.

Apoptosis is a form of gene-controlled programmed cell death that occurs in multicellular organisms [53,54]. It plays an essential role in embryo development and morphogenesis, and thus in the construction of highly ordered physiologic structures, the elimination of damaged or aging cells beyond repair, and the prevention of excessive proliferation of tumor cells.

2.3. The self-healing system

As one of its most amazing gifts, the human body possesses an enormous, miraculous, and persistent capacity to heal itself: the so-called "self-healing power." The body's self-healing power is manifested on at least three levels:

(1) **Cell and tissue renewal and regeneration.** Even when a large number of cells are destroyed, the surrounding cells replicate to make new cells, thereby quickly replacing the cells that were destroyed. Tissue regeneration can be seen in the liver, intestinal lining, bones, lungs, and many other areas [55–57].

(2) **DNA-repair machinery.** The human body possesses DNA-repair machinery for editing and correcting damaged or mutated DNAs to restore their normal structures and functions [58,59]. There are also processes in the body that maintain the quality control of protein folding by refolding or eliminating the misfolded proteins that frequently occur inside of cells due to mutations in the amino acid sequence or disruption of the normal folding process by external factors [60–62].

(3) **The ability to compensate for the loss of physiological functions due to damaged tissues or organs.** When the body's natural healing power declines, entropy generation is increased, which is accompanied by pathogenic and aging processes. However, prior to the occurrence of these events, the body can initiate its compensatory mechanism to maintain impaired physiological functioning to a certain extent. Heart failure is a typical representation and example of structural and functional disorderliness or a high-entropy

state [63]. Numerous factors contribute to heart failure syndrome, including a loss of muscle, decreased myocardial contractility, pressure or volume overload, and restricted filling, among which systolic dysfunction manifested by diminished ejection fraction is the most common heart failure syndrome. As the heart begins to fail, a number of compensatory mechanisms are activated. These include increased heart rate, the Frank-Starling mechanism, increased catecholamines, activation of the renin-angiotensin system, and the release of atrial natriuretic peptides, which initially help the heart to preserve its function [63].

The body's tissue-regenerating capacity is mainly conferred by stem cells and fibroblasts [55–57,64,65]. Pluripotent stem cells can replicate themselves and differentiate into any cell types that are needed. Stem cells in the human body include hematopoietic, bone marrow mesenchymal, neural, liver, skin epidermal, intestinal epithelial, retinal, and pancreas stem cells. Fibroblasts play an essential role in cell proliferation in the wound-healing process and the formation of the intercellular matrix. As mentioned more generally above, DNA-repair enzymes are responsible for DNA repair, and molecular chaperones such as heat shock proteins handle misfolded proteins.

2.4. The anti-wear-and-tear system

Allostatic load, or "the wear and tear on the body," is a damaging factor that accumulates as an individual is exposed to repeated or chronic stress, which naturally and inevitably occurs in the parts of an organism or in the tissues and organs of the body as a result of their normal usages, even with care and proper maintenance [66,67]. The phenomenon of wear and tear reflects the second law of thermodynamics: Objects stray from their original form and function over time unless energy from an external force is used to maintain them. Such deterioration imposes persistent yet slow destructive pressure to the orderliness and integrity of the architectures and function of the involved tissues and organs. This abrasion is manifested through the excessive use or abuse of tissues and organs, resulting in their functional and structural overload.

The "use or disuse theory," also known as "use it or lose it," explains that the parts of an organism that the organism uses the most will undergo hypertrophy and become more developed [68,69]. In contrast, the parts of the organism that are not used as much undergo atrophy and begin to degrade from lack of use. To maintain proper self-organization and metabolism, self-defense, and self-healing so as to sustain life, the tissues and organs of the body must function ceaselessly. However, constant functioning will undoubtedly evoke the wear-and-tear process. Fortunately, the human body possesses an innate resistance to wear and tear, and exhibits remarkable wearability and resilience. Its anti-wear-and-tear mechanism enables the body to resist and automatically repair the wear and tear that occurs in tissues and organs with daily physiological activities. However, when the rate of wear and tear exceeds the body's capacity, collapse of the body's orderly structures and an increase in its entropy ensue. Intriguingly, the wear-and-tear theory, as one of the theories on the human aging process, holds that aging is the result of the accumulation of wear and tear in organisms over time.

"Wear and tear," rather than "use it or lose it," has been employed to explain brain aging, Alzheimer's disease, and the role of proteostasis derailment in cardiac aging and disease, along with many other diseases [69,70]. For example, weight-bearing joints and joints that undergo repetitive stress and excessive wear and tear are particularly prone to developing osteoarthritis. This finding has been ascribed to the fact that cartilage has a poor regenerative capacity, as cartilage that is regenerated by stem cells fails to fully recapitulate the structural and biomechanical properties of the native tissue, even though stem cells can be differentiated into chondrocytes *in vitro* or aid cartilage regeneration *in vivo*.

3. Concluding remarks

The law of entropy increase is universal and unidirectional in all systems (whether isolated or open), although the process can be inverted to be bell shaped with decreasing entropy during the early stage of development and increasing entropy during the aging process in living systems. From a thermodynamic point of view, entropy increase that leads to the loss of a low-entropy state is an undermining force that drives the deterioration of structural and functional orderliness; in this way, it is the common mechanism for the development of disease and aging in humans, regardless of different etiologies. Maintaining a low-entropy state is therefore the key in preventing and reversing pathological processes of all kinds. In fact, the human body is naturally equipped with low-entropy-safeguarding mechanisms composed of the self-organizing, self-defense, self-healing, and anti-wear-and-tear systems. Degeneration or disruption of any of these four systems will surely lead to eventual loss of the body's low-entropy state.

Unfortunately, for the time being, no "magic pill" exists for clinical intervention to maintain or restore a low-entropy state so as to maintain healthy conditions. Furthermore, it is not anticipated that any medicine or medical tools can be invented to help people maintain a low-entropy state in the future—or, at least, in the near future. This is because the entropy level or state in living systems is determined by multiple complex factors. The four systems described herein are the core and key controllers of the body's state of entropy, and a single intervention cannot affect them to a sufficient extent to drastically change the entropy state. Instead, maintaining a low-entropy state is a matter of adopting a healthy lifestyle in a persistent manner. One example of such a healthy lifestyle is a low-energy diet to reduce "entropy" intake and constant physical activities to enhance "entropy" discharge. Conceptually, preserving the wholeness and integrity of the body's self-organizing, self-defense, self-healing, and anti-wear-and-tear mechanisms by any healthy and efficient means is the ultimate solution for maintaining the low-entropy state of the human body.

In the future, however, it might be possible to utilize certain specific means of intervention to counter entropy increase. Studies have discovered that the activation of nuclear factor (NF)-κB during aging and the development of diseases plays a critical role in mediating age- and disease-related increases in cellular entropy, as manifested by DNA damage, chronic inflammatory response, increase in apoptotic resistance, decline in autophagic cleansing, and tissue atrophy [71,72]. Several longevity factors act as inhibitors of NF-κB signaling and thus can suppress the NF-κB-driven entropic aging process [71,72].

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