The New Science of Health

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Abstract

Significant prevalence of numerous diseases still dominates all global societies; it is an enigma why so much illness exists while so much is known about health. The purpose of this study is to explore the dilemma.

Material and Method: Public domain records, related to biologic systems in health and disease, have been studied. Systems Science and the Dynamic Systems Model methodologies were used as they offer corresponding methods for the examination of living systems in any state of health.

Results and Conclusions: Relationship with self determines who we are and how we relate to others; it is triggered by our decisions, which shape our behavior and lifestyle, recurring again as a frame for our new sensory input; this cycle reflects our evolving cognitive and epigenetic memories that formulate our ongoing reality. Health, within this framework, represents a global measure of cognitive and physical fitness, one that creates our intellect and the ultimate epigenetically-driven morphology.

Keywords: Health; Systems Science; Cognition; Decisions; Memory

Introduction

*Everything has to be examined, to reveal its meaning, in relationships to the whole. Alexander von Humboldt [1].*

The infinite potentialities of our Nature and the known Universe are condensed into ‘realities’ once observed, filtered by senses and crystalized as perception; the ‘realities’, however, are not uniform for all biologic systems as individual perceptions vary greatly; same genome but differing epigenomes, same brain but variable cognitions.

The perplexing mystery, about the prevalence of disease and disability in a society, is not that it exists but why it exists to such an extent in spite of the fact that so much is already known about health; the reasons that much is ignored can be found in our choices and decisions as they emerge from our personal ‘realities’.

This study differentiates data from information and from knowledge [2]. For a biologic system, ‘data’ are simply unconnected bits of encountered change that trigger our senses; ‘information’ represents connections among some data points which form patterns; and ‘knowledge’, our sensory perception, is the final understanding of what really happened.

An analogy of the above can be seen in the night sky: stars can be seen as data, constellations as patterned information, and knowledge is the realization of where we are, how we fit into it all, simply the final understanding.

Similarly, in this research, individual scientific articles were considered data, finding what united some of them was seen as patterned information, and figuring out what it all meant, in an aggregate, lead to knowledge.

**Material**

The period from 1960s to the present has been selected for the study of public domain records in the context of systems science and their possible relevance to health. In addition to scientific articles, general public domain publications were also selected, especially ones describing characteristics of larger societal systems. The collected information was grouped by similarities or dissimilarities with systems science principles. For example, for entropy, reports of decline and diminishing functionalities of systems were extracted; for chaos, publications highlighting exponential excess of unmitigated growth without differentiation, were mined. For systems in health territory, descriptions of optimal adaptation and evolution were also examined.

Research questions guided the literature search in this study. Explanatory publications (considered data) for specific categories (seen as patterned information) of this research, are listed below in order to enhance the understanding of the relationships among disparate observations and the connecting systems science.

**Methods**

Systems science methodology, originally conceptualized by von Bertalanffy, was selected for this study as it differentiates between healthy and unhealthy systems, those with the highest capacity to adapt and evolve with change, and those with the least [3].

In general, most scientific literature describes linear causality, 'you do this, and you get that' (excluding just about everything else); systems science looks at many published observations and asks: is there a pattern/relationship among the articles that may reflect some aspects of multi-dimensionality of Nature as the ultimate model for systems science?

The Dynamic Systems Model, also used in this study, was designed to extract meaning from any encounter of change by a biologic system. The Model defines three zones: the health territory, chaos, and entropy; it complements systems science because it places systems of various complexity states in a multi-dimensional assessment pattern. Such a mosaic allows for a more accurate creation of meaning from any perceived change as component parts often reveal the condition of the whole [4,5].

While studying diverse publications, listed in references, several themes began to emerge and the search focused on finding connectivity/inter-relationships among observed themes, especially those that were judged to enhance, and those that were thought to be detrimental, to health. The findings, pertinent to individuals as well as larger collective/societal systems, were reflected on the human body model for familiar comparison. The research also explored pathways that allowed not only a state of health to regress into illness but potentially reverse the path from disease back to health.

**Research questions**

Is there a difference between health and health care? Is the state of health deterministic or does it respond to our choices? What is the impact of time on biologic systems or do biologic systems impact time? What role does neuro-net play in health and disease and what are its key components?

**Results**

The following systems science principles were found to be highly relevant to the understanding of the state of health of biologic systems:

Relationships (with self and others) that are functionally healthy, also create similarly healthy structure; relationships depend on boundary, decluttering/recycling, communication, and hierarchy (horizontal and vertical); in combination, these characteristics create complexity (organized or disorganized) via networks (neuro, cellular), and ending as an emergence/outcome (from components/data, patterned information and knowledge creation); all such steps are implemented via decisions into interdependent processes of multi-

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plication-differentiation and cycles (reliant on biologic time). Dynamic Systems Model is capable of distinguishing healthy/differentiated systems from unhealthy/undifferentiated ones.

Key findings: Health is strongly related to ‘focus, fitness, and intellect’ that impact, on a cellular level, ‘stem cell-daughter cell’ cycles with efficacious balance between multiplication and differentiation, and, on the cognitive level, the signal transmission within the synaptic neuro-net where the ‘excitation and inhibition’ process is optimized.

Healthy systems manifest cognitive as well as cardiopulmonary fitness. This can be achieved through interval training: a) - periods of 80 plus percent increase in intensity of movement (also generates endorphins/endocannabinoids), b) - similar repetitive timeframes with food intake limitation, caloric restriction (which up regulates longevity genes, SIRT1), and c) - comparable intervals of sustained focus of sensory perception arising from inhibitory synaptic influence on all other input (which clarifies thoughts). Such a treble-focused program allows biologic systems to reach the ‘inner aspect of chaos’, within the health territory of the dynamic systems model, where the expansion of ‘muscle-brain’ intelligence has the best chance to succeed as new health.

Answers to research questions

There is a fundamental difference between health and health care; the first, health, is an emergence/outcome/end-product of each individual biologic system's decisions and lifestyle choices; the second, health care, is a self-maximizing business system.

Health is deterministic primarily through our choices which shape each epigenome that is responsible for physiology and morphology of each biologic system and has a transgenerational reach.

Biologic time, the period from the beginning to the end of a given biologic cycle, is critical to biologic system's health; it is bidirectional in contradistinction to linear and non-reversible chronologic time.

The synaptic neuro-net has an optimal range of sensory processing when it emphasizes the dominant role of inhibitory neurotransmitters that protect cognitive threshold and assure cognitive reserve; any prevalence of excitatory signals, processing input via the reward pathway, and/or dysexecutive syndrome of the prefrontal cortex, strongly points to the state of ill-health.

Discussion

All living entities exist within a complex adaptive system that we call Nature but not all are optimizing participants. Smaller systems, including us, should proactively adapt and evolve, not in linear but ecologically-dominant fractal patterns, demonstrating self-similarity and self-affinity, along with the rhythm/cycles of Nature. Healthy, cognition-endowed systems, are not genetically programmed to remain healthy but must make appropriate and concurrent decisions that favor organized relationship complexity that is capable to generate healthy emergence; in turn, this sequence contributes to healthy Nature while also sustaining individual living systems in health.

Overview

Human body is an example of a living entity that encompasses the potential to be the best individual complex adaptive biologic system, analogous to the largest such a system, Nature. Human being is not to be understood in linear, mechanistic, deterministic, and time-dependent fashion; it is not analogous to a car. Healthy system goes through the engagement of all of its parts in learning which is provided by bi-directional feedback loop relationships, through semipermeable boundaries; relationships need to follow the system's internal as well as external cycles; a healthy system has a balanced intake-throughput/metabolism-output sequence of an open system with ongoing decluttering/recycling of each of its subsystems, and with an overall goal of creating value as its output; such value needs to include, in an aggregate, efficiency, effectiveness, risk management, and proportionate cost; simultaneously, healthy body is also an optimizing contributor to the larger ecologic cycles (see Figure 1).

Human body has evolved not only to move but also to think, a mutuality of muscle-brain interaction; both muscle and brain have their specific function and structure that is responsive to our decisions. The reliance of all components on one another, their inter-relatedness and bidirectional inter-operable communication in healthy systems, have the capacity to adapt and evolve; as the created complexity of cognitive systems rises, however, so does the potential for disharmony and malfunction, seen as disorganized complexity; this is due to non-optimizing decisions. Systems science provides, in real time, an understanding of the above intricacies, and offers the concepts as the new science of health (see Figure 2a,b).

**Figure 1:** Existential phases of biologic systems with considerations for health sustainability.

**Figure 2a:** Sustaining health with muscle-brain training.
Healthy biologic systems, with their primacy of function over structure, are the consequences/outcomes of what we think and what we do. Controlling unhealthy behavior has proven difficult throughout history [6].

Our decisions are the outcome of sensory processing and perception by our neuro-net. Optimal functioning of neuro-net depends on a healthy state of all its components: senses, capacity for input filtration and compression in order to protect our limited cognitive threshold that is essential for healthy decisions, and the engagement of 3-D hippocampal memory and the executive prefrontal cortex. In an aggregate, such a neuro-net functional sequence formulates our memories, cognitive as well as epigenetic, which can be either healthy or unhealthy; in return, such a state influences the creation of our future decisions in an endless feedback loop; how we ‘perceive’ is how we ‘see’.

Not only our decisions communicate with our body, via epigenetic influence, but, similarly, our bodies communicate with us as well with parallel, though delayed by time, morphologic alterations; listening to such a dialogue requires health intelligence, one that creates a concordance between what we are telling our body with our choices, and what the body understands and, in response, is telling us; morphogenic messages from the body represent a long-term epigenetic memory that is more significant for our health span than our short-term cognitive memory.

Health is not health care; health is an emergence, a dynamic outcome of adaptation and evolution of a biologic system with change; current health care is just a business where its components maximize themselves without optimizing the larger societal system [7].

Living entities experience fluctuations/cycles in their function and structure that determine the biologic time that is not fixed by Earth’s axial rotations; only the circadian oscillation is related to the movement of Earth due to the presence or absence of light. The magnitude of influence of circadian rhythm/clock on human body can be gleaned from the fact that just about every cell contains receptors that are responsive to this cycle.

Figure 2b: Sustaining health with expanded training of muscle and focused sensory processing.
Cycles allow for the balance of activity/excitation and recovery/inhibition of various biologic processes, which are all dependent on the following complementary sequences: day-night oscillations, metabolic sequences, sensory processing, interdependent supply-decluttering, etc.

Details/Specifics

The term relationship, within systems science concepts, defines the character of system’s functional complexity, which, if healthy, should exhibit an amalgamation of reciprocity, fairness, empathy, and trust, an organized complexity; both relationships and complexity evolve from our decisions and can be either system optimizing/organized/pro-health or system non-optimizing/disorganized/unhealthy.

Health depends primarily on our relationship with self, expressed in a level of focus, fitness, intellect (recognition of cognitive threshold, decisions regarding diet, and stress management via avoidance of cognitive dissonance).

Focus evolves from prioritizing a chosen sensory processing; it demands the following: living in the engaged existential time frame, putting aside the impediment of chronologic time for a chance of creativity, and seeing the still-unexplored connections in the larger system of Nature; during focus, the perception of chronologic time ceases to exist due to an optimizing experience; it resembles a state, sometime referred to as being in the “FLOW”, meaning now, neither tomorrow nor yesterday [8] (see Figure 3a).

Cognitive focus implies a concentrated attention on a task allowing data to be processed in a continuous manner by the neuro-net thus increasing its efficacy; such a peak performance reflects the fact that only one sense can perform at its best at a given time. For example, when hearing is engaged in a continuous stream, its performance is efficient but when a visual processing is added, hearing suffers. Saturating cognitive threshold with a visual task impairs the brain’s response to sound. During multi-tasking not only sensory processing but even perception takes place in discontinuous fashion resembling waves of different frequencies which create interference among them and alter the relationship between space and time [9,10].
The continuous sensory processing and perception, during focus, minimizes errors of synaptic connectivity; healthy systems correct errors quickly; unhealthy systems struggle with errors and they last too long. The plasticity of synapses that streamline transmission can be pharmacologically affected. For example, caffeine increases synaptic plasticity by antagonizing adenosine receptors [11,12].

Selective attention enhances the corresponding neural responses and is characterized by inhibitory alpha-band (approximately 10 Hz) activity in temporal response function; it switches between attended and unattended objects every approximately 200 ms, suggesting a sequential sampling even when attention is required to stay on one object; the switching pattern correlates with attentional behavioral performance; selective attention involves a dynamic mechanism for monitoring all objects outside of the focus via series of attentional chunks [13].

It has been observed that when people do two cognitive tasks at once, their cognitive capacity can drop from that of a Harvard MBA to that of an eight-year-old; such a drop in performance is called dual-task interference [14].

Filtering out an input and protecting cognitive threshold are the keys to focus. As stated: Those who get ahead will be the folks who figure out what to leave out, so they can concentrate on what’s really important [15].

Fitness can be measured and encompasses: endurance, speed, strength and flexibility; historically, it is this capacity that allowed biologic systems to survive; on a metabolic level, it reflects how efficient the biologic system is in using oxygen and glucose, the essential components of both muscle and brain metabolism (see Figure 3b).

![HEALTH sustainability prerequisites & functional goals
Fitness: endurance, speed, strength, and flexibility & enhancement with intervals of a) 80+% increase in movement and b) caloric restriction](image)

**Figure 3b:** Fitness.

On a cellular level, high-intensity interval training, for example, is capable to reverse the age-related decline of mitochondrial-energy producing function (between 49-69 percent) and protein-building capacity of ribosomes in muscles; it also improves insulin sensitivity; it is stated that vigorous exercise remains the most effective way to bolster health as it also increases maximal oxygen uptake and delivery (measurable as V0₂ max) and maximal stroke volume. Older adults who scored high on cardiopulmonary fitness (CRF) tests performed better on memory tasks than those who had low CRF; memory performance and brain activity largely paralleled studied-subjects fitness level [16-18].

Exercise-induced endorphin/endocannabinoid release in the brain also depends on the intensity of exercise, which might alleviate the stress caused by the high-intensity exercise through controlling pain and emotions. A less demanding, e.g. traditionally recommended one-hour aerobic exercise, does not cause similar endorphin release. Quoted study points to a pathway that may control drug addiction with high intensity training as it generates the same opioids in the brain [19].

It has been observed that the neuro-net functional connectivity in runners as well as musicians is greater than in non-runners and it also correlates with body mass index and achieved educational level [20].

Statistically, the expected longevity is shortened by about 42 percent among people who are not fit representing a similar risk that has been associated with heavy smoking [21].

Laboratory experiments with *C. elegans* show that it is the speed of movement (analogous to walking speed in humans) that is quite an accurate predictor of longevity [22].

Simple increase of one hour per week of vigorous physical activity was found to be associated with a 0.31 percent longer leukocyte telomere length, a marker of a healthy biologic age [23].

Similarly, greater muscle strength is associated with better cognitive function in studied population with an average age of 66 years [24,25].

Firmer and fitter bodily frame is linked to firmer and fitter brain with a more elastic hippocampus indicating that more aerobically fit individuals have better memories; both atrophy and reduced size of the hippocampus have been previously observed in cognitively declining seniors and developmentally delayed children; the current finding of firm body-firm brain connection comes from MRE (magnetic resonance elastography) examination, which provides a qualitative measure of adjustments associated with function of the hippocampus; this new imaging technique gently ‘bounces’ an organ, in this study the hippocampus, and measures how it responds; it is done with a pillow under the subject’s head that generates harmless pulses, known as shear waves that travel through the hippocampus. MRE instruments measure how the pulsed waves undergo modifications as they move through the brain and those give an extremely accurate measure of the elasticity of the tissue; those with higher fitness levels had more elastic hippocampus and scored the best on memory tests [26].

Intelligence does not equal education but usually leads to it; intelligence is understood as the ability to solve problems previously not encountered; it emerges after possessing core knowledge about Nature; intelligence is based on a healthy memory-prefrontal cortex complex that is able to ask rational and meaningful questions followed by pragmatic responsibility [27-29] (see Figure 3c).
People use opinions, not facts, to make decisions and then use rationalization again to justify them to their cultural/social cluster, trying to influence how others see them, e.g. reputational management [30].

In general, it seems less important what you eat than when you eat, implying that the metabolic cycle, started by any food intake, should be within the day phase of the circadian oscillation; otherwise, it disrupts the circadian cycle due to their inter-relationship and altering dominance; also, intervals of caloric restriction are highly preferable to excessive intake.

Diet has to include sufficiency of vitamin A, which protects stem cell activity-hibernation cycle (this cycle of activation and hibernation must be preserved to avoid uncontrolled production of immature cells, such as in leukemia). Retinoic acid, an active metabolite of vitamin A, allows the active stem cells to return to a dormant state/hibernation and conclude their own end-stage differentiation. Cancer stem cells, like healthy stem cells, also rest in a state of dormancy with near zero metabolism; vitamin A not only enhances cell differentiation but also balances the excitatory-inhibitory synaptic transmissions, primarily via gamma amino butyric acid (GABA) neurotransmitter (deficiencies in GABAergic neurons have been associated with several neurological disorders, including Huntington’s disease, autism, schizophrenia, and epilepsy); chronic, immune-related, inflammation lowers the level of retinoic acid [31-35].

Sufficiency of vitamin D should be achieved with both food intake and exposure to sun light, as vitamin D is a key contributor to DNA functioning. Vitamin D is first metabolized into 25 hydroxyvitamin D (25OHD) and then to the hormonal form 1,25-dihydroxyvitamin D (1,25(OH)2D), the ligand for the vitamin D receptor (VDR), a transcription factor, binding to sites in the DNA called vitamin D response elements. There are thousands of these binding sites regulating hundreds of genes in a cell-specific fashion [36].

Adequate vitamin C intake is important for the epigenetic process of DNA de-methylation (oxidation) allowing stem cells, within bone marrow, to mature and prevent cancer development (leukemia, lymphoma, some solid tumors) [37].

Overall, any caloric excess is unhealthy, as it is only caloric restriction that UP regulates the longevity gene SIRT 1 while metabolic excess DOWN regulates it, leading to a shorter life span; similarly, mitochondrial metabolic imbalance is unhealthy as it often leads to cancer [38].

Stress is primarily about our interpretation of what is happening, how it impacts our existential level within Maslow’s Pyramid of Human Needs; this pyramid can be modified to only three basic levels: safety/security, sense of belonging, and self-actualization; the degree of health, existing among people whose lifestyle approximate a specific level of the pyramid, is a reflection of epigenome modifications by decisions prevalent at each level of a cultural cluster [39].

Stress management, as part of systems relationships, must emphasize the path toward resolving any cognitive dissonance while simultaneously protecting cognitive threshold. Healthy systems adapt and evolve with change, which they convert, via senses, into a quantifiable risk; unhealthy systems perceive change mostly as unquantifiable uncertainty generating stress through cognitive dissonance. Though diet and exercise are important for health, the greatest contribution likely comes from managing stress [40].

Healthy relationships create communication that is inter-operable among all engaged systems; for each, it begins with the translation of the electro-chemical signals, generated by the neuro-net processing, and ends as the silent internal cognitive chatter, understanding/perception, of the mind that is coherent and reflects system’s organized complexity; unhealthy relationships demonstrate the opposite.

All communications are multidimensional including ones that are verbal and non-verbal, via mathematical symbols or musical notes, ionic, pH-related, membrane potentials, proteins, etc.; regardless of what a biologic system does or does not do, on some level, it all represents a form of communication.

For example, fatty liver, which increasingly produces glucose, unfavorable fats, and proteins can cause damage to other organs, such as pancreas or renal function via its chemicals, in this instance, negative/unhealthy communication. Approximately every third adult in the industrialized countries has a morbidly fatty liver [41,42].
Relationships within systems sequester into either a horizontal or vertical hierarchy, colloquially the people in the trenches/system components or the governing body. Balance between the two hierarchies needs to reflect mutual collaboration for the benefit of the larger system; basically self-organization needs to develop within the horizontal hierarchy and system-optimizing laws/regulations need to be generated by the vertical hierarchy.

A study of twins showed that those with shorter sleep duration had a depressed immune system; seven or more hours of sleep is recommended for optimal health; short-term sleep deprivation, in a laboratory setting, increases inflammatory markers and activate immune cells; chronic sleep deficit shuts down immune response of circulating white blood cells [43] (see Figure 4).

The American Automobile Association reports that missing 1 - 2 hours of sleep (having less than 7 hours of sleep), is quite consequential as it doubles automobile crash risk and is similar to driving over the legal limit for alcohol [44].

Sleep is essential for keeping memories; without sleep, memories are likely to be lost. During sleep, synapses of activated neurons are restructured; for example, in the mouse brain this process takes place every 12 hours as there is a limit, a threshold, on how much information can be remembered before the need for sleep and synaptic recalibration emerges [45].

Pleasure-signaling neurotransmitter dopamine also directly influences/suppresses the circadian center; aberrant dopamine neurotransmission has been reported with Parkinson's disease, depression, attention deficit-hyperactivity disorder, bipolar disorder, schizophrenia, obesity, cardiovascular diseases, drug addiction, and even cancer; all preceding diseases have the characteristics of entropy [46].

During memory consolidation, synapses produce new proteins that strengthen fragile memory traces; if, however, a new stimulation occurs during this consolidation period, the new stimuli could disrupt the consolidation process since the initial memory traces are fragile and only a small number will become long-term memories. The brain partially solves this problem by postponing some of the memory consolidation to a period in which new experiences are minimized; consolidation proteins are produced in greater quantities during sleep; on awakening, brain blocks long-term memory arising from the new stimuli [47,48].

Most synapses shrink during sleeps and grow again during the next awake period; shrinking offers the possibility of new growth during the next wakeful period [49].

The rhythmic excitation and inhibition at synapses makes memories permanent; memory needs to be not only acquired but it also needs to be stabilized through memory consolidation dominated by synaptic inhibition, which is the underlying mechanism that creates sharp wave ripples coming from the hippocampus [50].

We are our memories, cognitive and epigenetic, which are derived from our relationships with self and the world at large representing our reality, our narrative. It is not what the senses process but what we understand, what we perceive; our previous decisions made this process either healthy or unhealthy. Existing patterns of memory are recalled with any new event acquisition for a probabilistic pattern comparison. Such a fundamental memory-acquisition-recall sequence, however, immediately highlights the critical importance of memory formation by a given biologic system and is raising the following question: was an optimized hippocampus-prefrontal cortex relationship engaged? A healthy biologic system preferentially selects 3-D sensory input, known to form patterns of 3-D memory network within hippocampus. In contradistinction, an artificial 2-D sensory input, for example from flat TV screens, phones, simulators, etc., leads to a loss of 3-D memory network; any subsequent recall of such an inferior memory pattern, offers only a mediocre/unstable substrate for any probabilistic pattern comparison of any future sensory input. Also, if the preferential pathway for sensory processing is the reward centers route, then the prefrontal cortex, the executive decision center, is significantly handicapped to make healthy/optimized decisions, its emergence [51-54] (see Figure 5).

![Figure 5: Formation of reality.](image)

In this digital age, we electronically generate and receive sizable amount of data, but we do not remember it all; what transpired, what was encountered by cognition, is now delegated mostly to some digital storage, though the epigenetic memory does remember this disconnect quite well; the ‘digital age remembering’ usually means storage of data on a server and we remember only that it can be searched in some database (but, as is often said: how do you Google what to Google?); as a consequence, our biologic/cognitive long-term memory is not being concurrently developed and the neuro-net storage capacity is being filled with things not needed to be remembered (e.g. TV
show, games, etc.); the long-term consequences of this memory shift, from a biologic neuro-net to 'cloud' storage of 'zeros and ones', are not known at present; however, one should remember that the storage of knowledge of the entire known ancient world, the Royal Library of Alexandria in Egypt, the library of the Ptolemy dynasty (third century to 30 BC), was destroyed by fire.

Measuring external/chronologic time is done by various clocks that indicate the divisibility of Earth’s revolutions; biologic time runs internally within a biologic system and begins with the start and ends with the completion of a given biologic cycle that may or may not be concurrent with some chronologic time (it can be longer or shorter); currently, biologic time can be measured by various biomarkers (telomere length, methylation, etc). The biologic time ‘marches to the drummer/clicks of our decisions’ (e.g. when we get up, go to sleep, what and when we eat, how much we move, etc.), irrespective of day or night; biologic time is always changing but often represents decisions-altered phenomena.

A conundrum exists with the long list of ‘diseases of aging’ that broadly parallel the chronologic time. This list, however, could reflect only the fact that the majority of societal cohorts make similar, mostly unhealthy, decisions, especially during their second phase of life, the phase of decisions, looking for Maslow’s ‘sense of belonging’; the magnitude of the decision-based epigenetic modifications, gradually but deterministically, assert their unhealthy morphologic imprints in the third phase of life, the phase of consequences; earlier decisions simply catch up. A financial metaphor may highlight the issue of aging as an accumulation of epigenetic debt; you start borrowing against your future health, starting in early adult life, but you never repay the loan, never correct the risk factors; then, in the third phase of life, the loan is called in. For example, one-third of US adults have cardio-metabolic disorders; glucose intolerance, insulin resistance, central obesity, dyslipidemia, and hypertension, are its key components [55-57].

How we perceive time is mostly related to our cognition. The past, the present, and the future are connected by memory, cognitive, and the epigenetic one, all coming into existence via sensory processing and perception; it is only the combined effort of hippocampal memory and the prefrontal cortex that creates understanding/knowledge of what we actually perceived. Decisions, expressions of consciousness, can propel us speedily into the future as non-healthy decisions rapidly age our bodies irrespective of the chronologic time that has elapsed since birth; healthy decision, however, can return us to a state of earlier chronologic years, allowing the biologic age to be younger than the chronologic time/age; the biologic age is the true measure of our state of health as it can go not only forward but also backwards due to the fact that it reflects the impact of our decisions on the epigenome which shapes our morphology.

Chronologic time is human invention; it stems from physical observations of the movement of planets; biology is different as it evolved only as part of Nature and thus follows its living cycles; chronologic time correctly records only the beginning and the end of a biologic system. Various biologic functions can be measured in chronologic time but the best you can get is a range because an absolute number is not very helpful; and, averages have no practical application as no one has ever lived 80 percent or died 20 percent [58].

Chronologic time is linear and, to a limited extent, is under the influence of our perception; it is strongly contextual; sometimes a minute seems like a second while other times it seems like an eternity. Erratic perception of chronologic time (of duration and sequence of events and their rhythm), irrespective of the clock face, can be observed in schizophrenia patients and represents errors in temporal information processing [59].

Strict constancy/regularity along chronologic time is not what healthy biologic systems experience; for example, if heart beats follow stringent regularity, it is a clear sign of danger. For example, ECGs of children have a very noticeable irregularity and such variability is also characteristic of a healthy adult; however, among older individuals, there is much less of this variation [60,61].

Healthy biologic systems need semipermeable boundary in order to participate in relationships that offer complementary emergence/output; examples of boundaries may include cell membranes, synapses within the neuro-net, endothelium within a vascular net, intestinal lining within the gut, skin, even clusters of culture/geography/history within a societal system, etc; each boundary has to be maintained in a specific functional state because once the boundary loses this selective functionality, system fragmentation occurs with a descend into chaos or entropy.
System boundary needs to be in a dynamic relationship with the intra- and inter-system environments; for example, healthy cells membranes, those in a semipermeable state, rely on an intraluminal acidic pH and a stable membrane-dependent proton gradients. Oxidative stress can impair cell membranes via damage to lysosomes; such a process increases membrane permeability as well as the accumulation of non-functionality; oxidative stress-responsive gene, the Lipocalin Apolipoprotein D (ApoD), an extracellular lipid binding protein, has antioxidant capacity and is necessary for lysosomes, a key cellular element to carry out the removal of detritus, in order to recover from oxidation-induced alkalization, both in astrocytes and neurons [62].

The blood-brain barrier, another example of a system boundary, prevents pathogens and toxins circulating in blood from entering the central nervous system; endothelial cells are its key components, which dynamically adjust to specific requirements [63].

Decluttering/recycling process plays a major part in health maintenance of biologic systems because clutter/detritus, on any level, represents stress; any accumulation of clutter indicates increasing non-functionality with proclivity of that system toward entropy; for example, the protein-making ribosomes and the protein recycling process, done via autophagy and apoptosis with detritus removal via lysosomes, are the active contributors toward healthy cellular balance.

The existential foundation of biologic systems, which allows for adaptation and evolution with change, is the synaptic neuro-net. It is this framework that develops cognition as its emergence, facilitating new sensory capture and processing, leading to new perception/understanding.

Optimized neuro-net is essential for the creation of organized relationship complexity which leads to pro-health decisions. Such a neuro-net evolves from the interaction of 3-D hippocampus with a well-functioning prefrontal cortex following sensory input; many synapses in this network receive their neurotransmitters via axoplasmic flow within the vagus nerve, from a healthy gut microbiome; the quality of the neurotransmitters and the microbiome is strongly influenced by lifestyle choices/decisions, which, in turn, create memories.

Influence on the neuro-net:
- Positive influence: healthy diet, fitness, stress management and cognitive reserve, among others.
- Negative influence: alcohol, obesity, inactivity, substance abuse, chronic stress, cognitive dissonance, saturated cognitive threshold, sleep deficit, among others [64-66].

Sensory processing, carried out by the neuro-net, is triggered by ‘movement’ and ‘intensity’ of any environmental change; the subsequent sensory perception, our understanding of what senses recorded, depends on ‘memory’ and ‘rhythm’ within the neuro-net. Our perception varies greatly; the interpretation of music by concert pianists is a good example of this variability of perception, as each incoming signal of sensory processing, each visible note, is literally different for each musician in spite of the uniformity of the printed sheet music.

Within the neuro-net, neurons are able to detect patterns and create a model of our environment while verifying which version of reality, which biases, support specific sensory perception. The initial data, triggering our senses, are available to perception but often simultaneously resemble multiple realities; the probability rule of a given perception then identifies the reality of current event that is accepted [51].

Malfunction of neuro-net has direct impact on health

The development of a ‘flat’ hippocampus, which is unable to create 3-D memory model, is strongly related to 2-D ‘flat’ sensory input from flat digital screens; ‘flat’ hippocampus is unlikely to support contextuality of decisions.

Prefrontal cortex, in a state of dysexecutive syndrome, creates non-optimizing decisions; it is frequently due to alcohol intake, lack of sleep, overwhelmed cognitive threshold, psychotropic drugs, etc.; such prefrontal cortex continues to select non-optimizing sensory attractors (those of either power or despair) from any new change-induced awareness (see Figure 6).

Use of reward pathway for sensory processing, via caudate nucleus, etc., mostly bypasses hippocampal memory; it generates neurotransmitter dopamine, which not only interferes with synaptic memory consolidation but also suppresses circadian rhythm; the subsequent decisions are grossly suboptimal (see Figure 7).

Figure 6: Dysexecutive syndrome.

Figure 7: Reward pathway of sensory processing.
All biologic systems are exposed to an infinite amount of stimulation, regardless of the sensitivity and specificity of sensory organs. Large volume of stimuli passes through various compression and filtration nodes of the neuro-net but in spite of that still has the capacity to totally overwhelm the perception.

The major contribution to the final understanding of sensory input, the perception, comes from the influence of inhibitory synaptic neurotransmitters such as gamma amino butyric acid (GABA); it facilitates differentiation of incoming signals.

The cognitive threshold represents a level of human sensory input beyond which comprehension rapidly declines; it is estimated that it is somewhere between 60 - 120 bits per second; generally, human speech is comprehensible at about 60 bits per second. The continuous loop of our silent cognitive chatter is probably around that number as well. Any daily experience will tell us that we can listen to and understand if one person is speaking to us but ask two people to talk to you simultaneously and the cognitive threshold is overwhelmed thus greatly diminishing understanding of either person. Similarly, we could have trouble understanding even one person speaking to us if our silent cognitive chatter has already saturated the cognitive threshold; the inhibitory synaptic neurotransmitters are exhaustible commodities that require production, transport, activity, and recovery. If the threshold gets overwhelmed/exhausted with indiscriminate 'noise' during sensory processing, e.g. watching excessive TV, any amount of additional data or information will not make it intact through the saturated threshold and subsequent decisions will carry that negative impact [67].

Cognitive reserve is considered to be the degree of available cognition before its threshold is reached; the degree of cognitive reserve influences dementia risk. Most dementias unfold over a long period of time, perhaps more than two decades. And, once dementia is diagnosed, as a gross manifestation of entropy/neuro-net degeneration, the subsequent decline is irrespective of previous level of cognitive reserve; an inverse association of dementia risk was found strongest with occupation, suggesting considerable plasticity in functioning up to at least midlife during which enriched environment affects cognitive performance rather than prevent loss in cognitive function, supporting the threshold model of cognitive reserve [68,69].

Systems science considers a society, organizations, etc. to be biologic systems in their own right; the principles for achieving health or losing it are the same as they are for an individual. For example, any saturation of the collective cognitive threshold, with white noise/irrelevant input, massively narrows the capacity for priority processing and perception, diminishing the ability of any group to make optimized/rational decisions [70,71].

A key to a healthy life is balance; balance between excitation and inhibition within the neuro-net and between cellular multiplication and differentiation. Inhibitory neurons are the key to coherence of sensory processing as they can enable a neural circuit to gate in specific pathways of information while filtering out the rest [72].

How fast or how slow we transmit data or multiply cells, either permits or hinders differentiation: for example, a change that generates sensory data can be morphed into patterned information; similarly, immature cells can be reframed into their target morphology. Both data transmission and cellular differentiation require a biologic interval for supportive processes to complete their cycles in order to allow the resupply of vesicular neurotransmitters into synaptic clefts or the maturing of young cells before another wave of new cells is generated by the stem cells (see Figure 8).
The inter-relationships between dominant function and consequential structure can be illustrated by the activity of nerve cells in the auditory system that has a direct morphologic effect on myelinization: higher levels of activity correlate with the formation of thicker myelin sheaths [73].

**Phases of life** can be broadly categorized into three groups based on similar characteristics of human function and structure within a societal cluster encompassing a life span. For example, the phase one begins at conception and extends into the early twenties; it is capped with the anticipated maturation of the frontal lobe, an essential foundation for decision making; the phase two and three largely parallel the expressions of culture within generational cohorts of adulthood and seniority that were previously identified by Howe and Strauss; the authors categorized the shared habits/lifestyles of rolling generations [74-76].

**Phase one, The Ancestral Phase: a transgenerational influence**

The function and structure of biologic systems, in health and disease, are a continuum, not only during their current existence but also as part of a transgenerational epigenetic influence. Parental behavior strongly influences a new offspring during its first phase of life as it further reinforces or modifies, already transmitted and often unhealthy, epigenetic modifications that were shared during conception. For example, among expectant mothers with high body-mass index (BMI), there is an increasing risk of major congenital malformations in infants; in a Swedish study of health registries, the risk for major malformations increased with increasing maternal BMI, recorded at the first prenatal visit, as organogenesis occurs during the first eight weeks of fetal development [77].

Epigenetic mechanisms, modulated by lifestyle, regulate DNA by switching genes on and off, activate or deactivate DNA sequences, and can be transmitted through generations as stored epigenetic memory in parents; mother also passes on the mitochondrial epigenetic marks to her offspring; the inherited epigenetic information needs to be healthy in order to correctly transcribe the genetic code in the developing embryo [78].

Prenatal ethanol exposure, from maternal alcohol consumption during pregnancy, can lead to Fetal Alcohol Spectrum Disorders (FASD), which may cause abnormalities in the brain and subsequent behavior, and also increases the likelihood of addiction later in life; this effect could persist transgenerationally [79,80].

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Parental physical activity or sedentary behavior of mothers was found to be directly correlated with the activity level of their preschoolers [81].

Similarly, childhood intelligence was found to be inversely associated with all major causes of death in adulthood. The 1936 birth cohort in Scotland was followed over the life course from age 11 to age 79 and documented this finding [82].

Our cognitive memories die with us or when the neuro-net degenerates; the epigenetic memory, however, lives on in our offsprings, at least through their first, ancestral, phase of life.

**Phase Two, Phase of Decisions: a cultural influence within a cluster**

The second phase of life encompasses most of our decisions. The impact of choices on the epigenome is well illustrated by the study of identical twins in Finland; they were initially raised together but, in adult life, during their phase of decisions, diverged in terms of the level of exercise. This divergence was eventually reflected in different bodies and brains, in spite of identical genes. The sedentary twins had lower endurance capacities, higher body fat percentages, and signs of insulin resistance, signaling the onset of metabolic problems; the twins tended to have very similar diets. The active twins had significantly more grey matter than the sedentary twins, especially in areas of the brain involved in motor control and coordination. Overall, among healthy adult male twins in their mid-30s, greater level of physical activity was associated with improved glucose homeostasis and modulation of striatum and prefrontal cortex gray matter volume, independent of genetic background [25].

Overall, the impact of unhealthy decisions is dramatic. For example, more than half of all cancer deaths in men in China in 2013 and more than a third of those in women were attributable to a group of potentially modifiable (with better decisions) risk factors, such as smoking, alcohol, nutrition, weight, physical activity, and infections [83].

Similar study demonstrated that following weight gain in adulthood, during the phase of decisions, the incidence of type 2 diabetes, hypertension, cardiovascular disease, cataracts, severe osteoarthritis, cancer, and mortality is increased in a dose-response fashion, and is greatest among those who gained 20 kg or more [84].

The feared neurodegeneration, clinically manifesting mostly in senior years, is preceded by a long history of unhealthy decisions during adulthood. The odds of having elevated brain amyloid, the characteristic component of Alzheimer’s disease, are increasing with each additional risk factor that participants, in the quoted study, had in midlife (obesity, smoking, hypertension, diabetes, and elevated total cholesterol) [85-87].

Holmes and colleagues write that even moderate drinking is linked to pathological changes in the brain. Studies using Mendelian randomization do not support the original claim that moderate drinking improves cardiovascular health. Alcohol use has been found to be associated with reduced hippocampal volume in a dose dependent manner; even moderate drinkers were three times more likely to have hippocampal atrophy. Higher alcohol consumption was also associated with reduced white matter integrity and faster decline in lexical fluency, a test of executive function. Alcohol dependence is already established as a major cause of dementia. The alcohol related brain damage typically involves relatively young people, often in their 40s or 50s; even light drinking increases the risk of various malignancies [88].

Negative epigenetic modifications can be seen in the shortening of telomeres, which signal cells that their genetic material has been compromised, often by lifestyle choices; telomeres can be measured and the length is considered to be an approximate level of biologic aging.

**Phase Three, Phase of Consequences: momentum from Phase Two continues**

Literature provides little support for the hypothesis that mental or cognitive training, during senior years, reduces the rate of cognitive decline; this observation is likely due to the fact that cognitive training was administered late, during the third phase of life; the progressive decline of cognition is the outcome of decisions in mid-years, during the second phase of life and fully expressed in the senior phase of life [89].

A window into the aging process, during the last phase of life, can be gathered form laboratory research. For example, stem cells in hypothalamus govern how fast aging occurs in the body as hypothalamus regulates growth, development, reproduction and metabolism; usually, the number of hypothalamic stem cells declines over the life of the studied animal; this decline accelerates aging but the effect of this loss is not irreversible. By replenishing these stem cells or the molecules they produce, it is possible to slow and even reverse various aspects of aging; hypothalamic stem cells release microRNAs (miRNAs) into the cerebrospinal that can be measured [90] (see Figure 9).

Telomere shortening and reduced cell divisions are considered hallmarks of aging and inform cells of errors in their genetic material, but not that simply their ‘time has come’. The damage of the genetic material did not happen in isolation or as a consequence of Earth’s revolutions, reflecting chronologic time, but most likely represents epigenome modification based on choices/decisions/lifestyle [91].

**Dynamic Systems Model: separating healthy from unhealthy systems**

Dynamic systems model represents a practical application of systems science to the assessment of living systems. The model defines three possible states: the health territory, zone of chaos, and the zone of entropy.

**Health territory** is conceptualized to include the inner aspect of the zone of chaos and the outer rim of the zone of order/entropy; on one hand, the disequilibrium of the inner aspect of chaos, within the health territory, is needed to avoid system’s deterioration into an unsustainable level of equilibrium; on the other hand, the outer rim of the zone of order/entropy is also contributing to the health territory and offers a degree of dynamic stability, an ongoing re-balancing of possible unhealthy extremes; examples may include physiologic irregularity of heart rhythm (representing the inner aspect of chaos) with boundaries (offered by the outer core of zone of order) thus keeping the heart rate within a sustainable range (see Figure 10a).
Optimized/healthy biologic systems, those in health territory of the model, generate mostly optimizing outcome/emergence that is available to other smaller or larger systems; as a consequence, more optimizing input is preferentially available to other optimized systems, which search for optimizing input, creating potential clusters of optimized systems; the opposite is true as well (see Figure 10b).

When the dynamic re-balancing between chaos and entropy, within the health territory, is lost, full chaos or entropy assert their individual dominance. The outer aspect of chaos is where pathologic irregularities take place, e.g. of heart rhythm, cell multiplication without differentiation or sensory processing engaging primarily excitatory over inhibitory neurons. The inner core of the zone of order represents a full-blown entropy, e.g. degeneration and ongoing accumulation of non-functionality.

The dynamic systems model can be used for analysis of function and structure of not only a single biologic system but a larger, societal one, as well. Societal systems are considered biologic systems that need to follow systems science principles in order to remain healthy; they demonstrate, as individuals do, the significance of clustered cultural decisions and lifestyle choices.

Collective intelligence, with rationality and responsibility, is present in healthy societal systems where its members make decisions based on prevailing scientific facts/evidence. Collective intelligence may not be present, however, within a framework of shared habits, opinions/views, behaviors, emotions, etc. that can be referred to as a culture; Maslow’s articulated a higher level of human need for the ‘sense of belonging’, which may explain this cultural tendency for imitations within a societal cluster.

The consequence of departing from systems science principles can be seen in societal systems, which eliminate, for example, boundaries in order to achieve economic integration (such as globalization); such societies are running the risk of social fragmentation/disintegration; the underlying driver of this phenomena, may be again a Maslow’s foundational basic human need for ‘safety and security’; if the above mentioned ‘sense of belonging’ is perceived to be disappearing, due to fully open/too porous boundaries, a strong movement will emerge toward smaller social clusters, where boundaries with some degree of permeability/control and thus safety, can be re-established.

As Tim Harford commented: economic integration allows political disintegration; if your country lets you down, make a new one [92].

Chaos

When a biologic system is within the main zone of chaos, attractors of power dominate the senses; such systems extract similar data for sensory processing and perception that manifest the power of exponential growth, cellular multiplication of immature cells without differentiation thus setting the stage for a likely outcome - a ‘cancer system’. In the microenvironment, differentiated cells begin to diminish due to the deterioration of the surrounding milieu (e.g. by smoking, etc.); cells with mutations take over leading to eventual cancer [93] (see Figure 10c).

It is the output that expresses the character of a system: a self-maximizing output indicates a system in chaos, which ‘generates and multiplies’ but ‘does not differentiate’. For example, mitochondria, a cellular sub-system, self-maximize in cancer cells [94].

Also, in a healthy cell, a dynamic balance of metabolic processes is established, in which most sugar is completely metabolized into carbon dioxide for energy production. In cancer cells this balance is shifted: sugar is no longer completely oxidized for energy production,

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**Figure 10c: Characteristics of biologic systems when in chaos.**
it does not complete its biochemical cycle, which is its differentiation, but, at that point, the metabolic intermediates are increasingly used for growth and rapid cell division [95].

When healthy patterns, encoded in the epigenome fail, differentiation stops but multiplication continues. Epigenetic regulation is disrupted in cancer with the following observations: dysregulated DNA methylation (hypomethylation or hypermethylation), histone modification (histone deacetylase inhibitors), and micro RNA modulation; the degree of hypomethylation of genomic DNA increases as a tumor progresses from a benign proliferation of cells to an invasive cancer [96].

The dominance of excitation, within the neuro-net, a process analogous to cellular multiplication, is also observed in systems that are in chaos; such systems primarily focus on generating new signals but without allowing the completion of their specific consolidation cycles that discriminate input, similar to the differentiation of cells. The formation of neural maps or differentiated morphology, relies mostly on inhibitory networks influence [97].

Entropy

Contrary to chaos, attractors of despair (depression, anxiety, etc.) dominate the sensory selection, processing, and perception creating a ‘degenerating system’; the main characteristics include: accumulation of non-functionality, due to the failure of decluttering/recycling process, which clinically spans from autoimmune and chronic inflammatory processes (type 2 diabetes, arteriosclerosis, malabsorption/gut disbiome, kidney, Crohn’s and celiac diseases, etc.) to neurodegeneration (Alzheimer’s disease, dementia, etc.), and neural tube birth defects (spina bifida, anencephaly) in mothers who are in entropy. What often accompanies entropy diseases is insufficiency of vitamin D, which is already suspected to have a role in multiple sclerosis, autoimmune disorders, infections, respiratory diseases, cardio-metabolic diseases, cancer, and fracture risk [98-106] (see Figure 10d).

![Figure 10d: Characteristics of biologic systems when in entropy.](image)

Epidemiological evidence suggests that sufferers from neurodegenerative disorders have a reduced incidence of most but not all cancers; for example, Alzheimer’s disease (AD) is associated with a 60% reduced risk of cancer, and a history of cancer is associated with a 30% reduced risk of AD; an exception is an increased risk for melanoma; this finding, however, is not surprising, as melanoma can be
thought of as a disease of entropy through its link to autoimmune diseases; overall, there is an inverse correlation between the risk of developing cancer and a neurodegenerative disorder [107-121].

It is not surprising that rapamycin, an immunosuppressive drug, which assists with cellular decluttering/recycling, can reduce cellular senescence (biologic states that can be categorized into entropy and linked to autoimmunity). Rapamycin helps to stop damaged cells from causing inflammation which often leads to not only neurodegeneration but also other degenerative diseases such as some cancers, heart disease, and diabetes [122].

Being overweight or obese, is a state of entropy, which causes mis-regulation of mitochondria and is associated with an increased all-cause mortality risk [123].

Similarly, aging is an entropy phenomenon as it causes cellular malfunction with diminished decluttering/recycling and dysfunction of the immune system [124].

There is a cross-communication between the neuro-net and the microbiome that has been suspected for over 100 years but only recently acknowledged as factual. For example, abnormal gut microbiome has been found to be associated with neurodegeneration and contributes to the microbiome-brain connection, which parallels the functional state of the entire biologic system in either health or disease. In the early 1900s, Elie Metchnikoff, a Russian zoologist, known for his Nobel Prize-winning work on the immune system, theorized that toxic bacteria in the gut caused aging and senility [125,126].

Healthy function/physiology generates healthy structure/morphology in biologic systems. Several examples follow: One, from neuro-net observations and two, from stem cell studies.

Neuro-net’s healthy functional emergence, optimal cognition, depends on balance between synaptic excitation and inhibition; GABA provides the dominant inhibitory influence when measured, for example, in the frontal lobe. Increasing age shows GABA decline, associated with poor cognition, reflecting functional insufficiency to inhibit excitation and sustain healthy cognitive balance; this dysfunction precedes morphologic changes observed as degeneration; GABA levels can, however, be increased by exercise [127].

When neurons reach their threshold, due to constant firing, they lose their capacity to convey information, representing a failure of data differentiation, impacting learning and memory. Among stem cells this observation is analogous to runaway multiplication that loses the capacity for cell differentiation [45].

Among seniors without dementia, faster cognitive decline, a clinically visible neuro-net degeneration, was observed to be associated with a decreased risk of cancer, a chaos disease; both entropy and chaos states usually cannot exist simultaneously [128].

Neurodegeneration, as seen in Alzheimer’s disease, could begin in utero or just after birth, if the fetus or newborn has a low vitamin A level, which is essential for neurons to differentiate streaming data/input into patterned information; studies of genetically-engineered mice, an Alzheimer’s disease model, demonstrate that supplements given to newborns with low levels of vitamin A could be effective in slowing the degenerative brain disease; mice, when deprived of vitamin A, performed worse as adults on a standard test of learning and memory; there is also some evidence, in humans, of the vitamin A - dementia connection in later years [129].

The development of unhealthy biologic systems with pathologic morphology can be preceded, initially, by excessive function; when stem cells enter such a phase, there is an inevitable shortening of telomeres; this process, mostly driven by epigenetic consequences of our decisions, shows fast cellular production that does not allow stem cells to complete their natural cycle of activity and recovery; such a process may continue into uncontrolled growth phase of immature cells, with cancer as clinical manifestation, short telomeres but higher telomerase (due to their ongoing attempts but inability to repair and lengthen the telomeres); if over-activity of stem cells is exhausted prior to reaching the clinical cancer state, they then enter regressive senescence phase observed as morphogenic degeneration; the first
phase, with dominance of speed in stem cell multiplication, represents a system in functional chaos, which may be followed by similar morphology (cancer); the second phase represents a system in declining functionality of entropy, followed by similar morphology (degeneration); both the first and the second phase epitomize unhealthy states of biologic systems. Unfortunately, both phases often follow one another, e.g. cancer develops and is eventually followed by full degeneration, i.e. chaos trailed by entropy without the system ever finding the balance of health territory; it is of interest that when the process of morphologic entropy/degeneration manifests first, it is unlikely that cancer, the morphologic state of chaos sequence, will follow; failing throughput can only lead to degeneration; cancer requires runaway function/multiplication [130].

Maintenance of intestinal permeability, a system boundary, is likely related to the reduction of inflammation and strengthened immune system, as measured by C-reactive protein and antimicrobial peptides; clinically, intestinal permeability measures ‘gut leakiness’ and is a known predictor for clinical relapse in Crohn’s Disease, an autoimmune disease of entropy. A clinical relapse was found to be significantly less frequent in those studied patients who received a high dose of vitamin D where zero percent experienced relapse; also observed was a significant improvements in anxiety and depression, likewise illnesses of entropy [131].

Vitamin D increases proteins involved in re-myelination in multiple sclerosis, in an entropy disease model; levels of 2’,3’-Cyclic-nucleotide 3’-phosphodiesterase (CNPase) and myelin oligodendrocyte glycoprotein (MOG) were significantly increased in the vitamin D injected mice [132].

Yoshinori Ohsumi won the 2016 Nobel Prize in medicine for work on autophagy, one of biologic systems’ decluttering mechanisms. Autophagy is the body’s internal recycling program; the process is crucial for maintaining a healthy metabolism in which cellular detritus is sealed in sack-like membranes, autophagosomes, and then transported to lysosomes. Failing decluttering/recycling process, as part of entropy, has been linked to neurodegenerative and autoimmune diseases [133].

**Limitations**

Systems science is not a theory, which should be subjected to falsifiability as a criterion of its validity; it should not be judged as such as no one can disprove Life and its wisdom; systems science is expressing principles observed in Nature and operational in all living entities. Systems science is a young methodology and the current conclusions will need to be verified with longer observations.

**Conclusions**

The New Science of Health is constructed as an explanatory approach to health, conceptualized as a result of our decisions and relationships. This method highlights the need for our understanding of what a biologic system is, its principles and their daily interpretations. The key to comprehending healthy intra- as well as inter-system relationships is the realization of the essentiality of bidirectional, feedback loop learning. The medium, inter-operable communication, visualizes the receptive listening of the entire bodily system, through all of its components, to messages received through consequences of our decisions and records them in the epigenome; the bidirectional communication, however, also requires our perceptive listening with meaning to the signals that the epigenome generates through morphologic and physiologic changes; a healthy biologic system must be aware of the significance of this bi-directionality of ‘us-initiated and decision-based’ communication that creates cognitive as well as epigenetic memory, our reality, and take proactive steps to create a healthy emergence.

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