

# The Essence of Health and Longevity

Ivo P. Janecka \*

Foundation for Systems Research and Education, New York, NY, US

\*Corresponding author: [ivojanecka@hotmail.com](mailto:ivojanecka@hotmail.com)

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**Abstract** The health of global societies is worsening; this is reflected not only in the increasing prevalence of co-morbidities in the population but also in already registered shortened lifespan. Systems science and the dynamic systems model have been used to study the core issues of unhealthy biologic systems, cascading down to cellular level. The still-evolving COVID-19 pandemic has exposed the vulnerabilities and spiraling penalties of unhealthy lifestyles. Dysfunctional immune system, a boundary, has been put in focus in this study, for its role in not only failing to protect but, through its components breakdown, also cause damage to the entire biologic system of human body; more than the 'virus', human decisions, and their impact on health, have been the significant upstream etiology of the pandemic because viruses favor unhealthy cells for their replication. The path to regain health, individually and collectively, is not in new drugs but in inculcating the importance of highly-structured decisions-consequences learning loop; in addition, interval training, spanning intensive physical exercise and selectivity of caloric and sensory input, benefits all levels of living systems-from cells to societies.

**Keywords:** *health, longevity, immunity, decisions, consequences, hierarchies, training*

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*And in the end, it's not the years in your life that count.  
It's the life in your years.*

Abraham Lincoln [1]

*Nobody ever did or ever will escape consequences of  
his choice.*

Alfred Armand Montapert [2]

and is highly uncertain as humans are not Nature's essential species.

It is this dichotomy that prompted current research, with emphasis on a path that can lead to both health and longevity. The knowledge, for reaching these targets, already exists, not just in scientific literature but also in general press; the understanding of why we don't take the, what Scott Peck's book title names the 'road less traveled', requires self-reflection with insight. [3]

## 1. Introduction

This research explores the evolutionary principle of optimization, a state of health, with a special focus on biologic systems. Humans are unique among all living entities in many respects but the most significant one is their continuing departure from this canon. It is perplexing to consider the existing societal conundrum that, while everyone wants both health and longevity, the vast majority of people today do everything possible not to achieve it. The detrimental effect on health that arise from behavioral and lifestyle choices, including smoking, obesity, alcohol, lack of sleep, and lack of physical activity, is well known but ignored, though, people's decisions-altered epigenome 'never forgets'. Humans are the only living species that accumulate massive number of harmful conditions and continue to exist, with over 2 billion, 25 percent of global population early in 21<sup>st</sup> century, obese including consequential metabolic diseases; also a well-known is the fact that obesity is healthier than smoking. Evolution's seeming permissibility of such a state, however, goes contrary to Nature's optimizing principles; the outcome of this incongruence is pending

## 2. Research Questions

What are the key functional and structural elements of biologic systems that directly impact health and longevity?

What are the essential health-related characteristics of these elements?

## 3. 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. In this research, individual articles were considered data, finding what united some of them was seen as patterned information, and figuring out what it all meant, the aggregate knowledge, was searched for within systems science principles.

### 4. Methods

Systems science methodology, originally conceptualized by von Bertalanffy in the 1960s, was selected for this study for its focus on extracting principles from observations of life. [4]

Systems science is not a theory, which one should seek to disprove as validation of theory's authenticity; it should not be judged as such; systems science observes life and attempts to understand its principles as well as its evolutionary experiments. [5]

Systems science explores life's principles on all levels and searches for coherence; it connects downstream research discoveries with their likely upstream significance. 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 patterned relationship, among studied articles that may reflect some aspects of multi-dimensionality of Nature, as the ultimate model for systems science? Systems science allows root-cause-analysis, literally, to the cellular level of a living system.

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 a human body model, a biologic system with many inter-dependent sub-systems with the capacity to generate value as a whole but not as a sum.

The dynamic systems model, also used in this study, was designed to categorize biologic systems while they encounter change. 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; in this model, the junction between health territory and chaos or entropy is where life's most acute adaptation and evolution or devolution occurs, it is where the 'seas are rough but islands of new life are born' or 'lost'. [6] [Figure 1a-d]

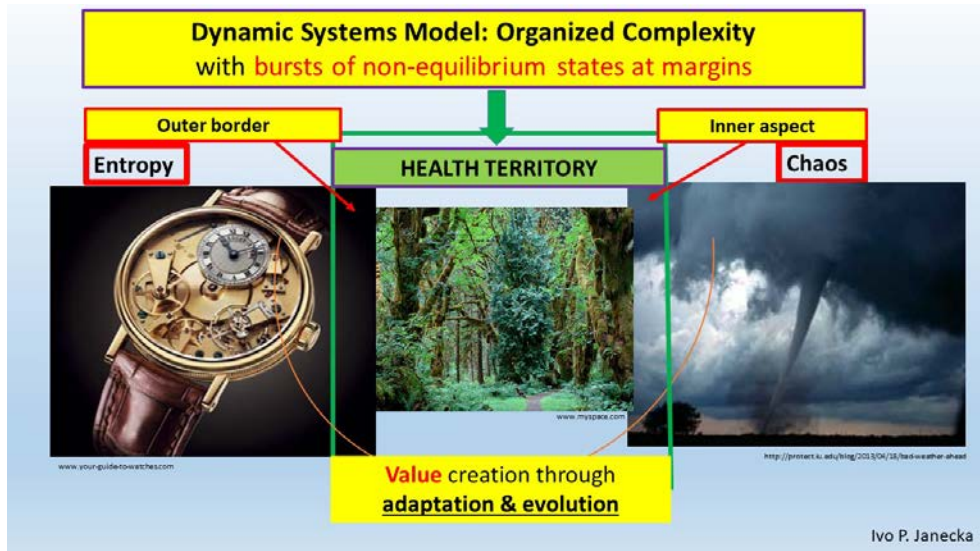


Figure 1a. Health territory (center), with chaos and entropy on each side, and overlapping areas

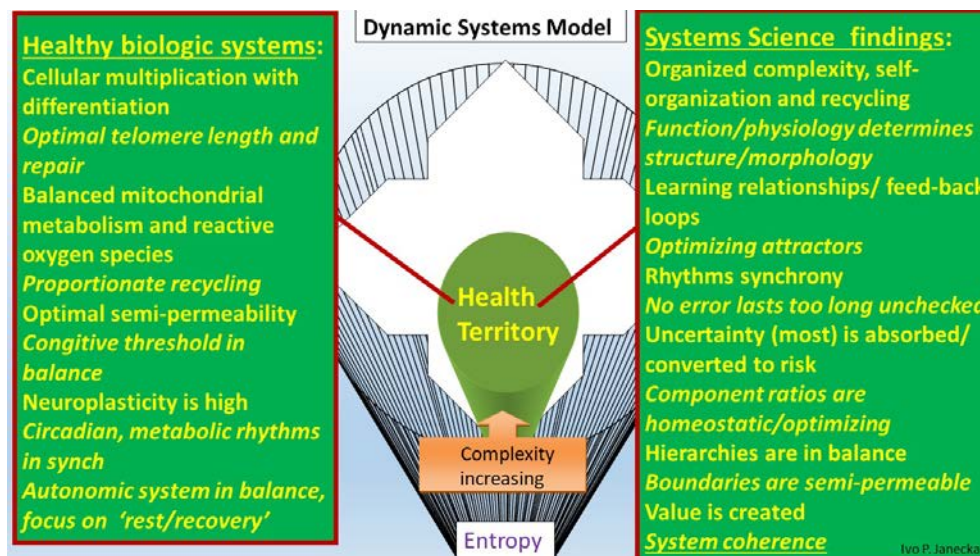


Figure 1b. Characteristics of biologic systems when in Health Territory

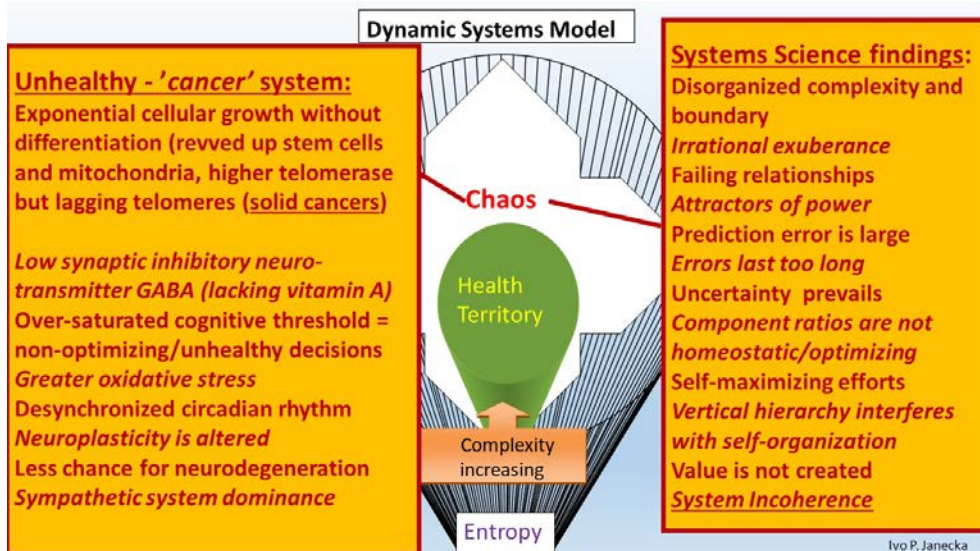


Figure 1c. Characteristics of biologic systems when in chaos - a 'cancer life' without a boundary'

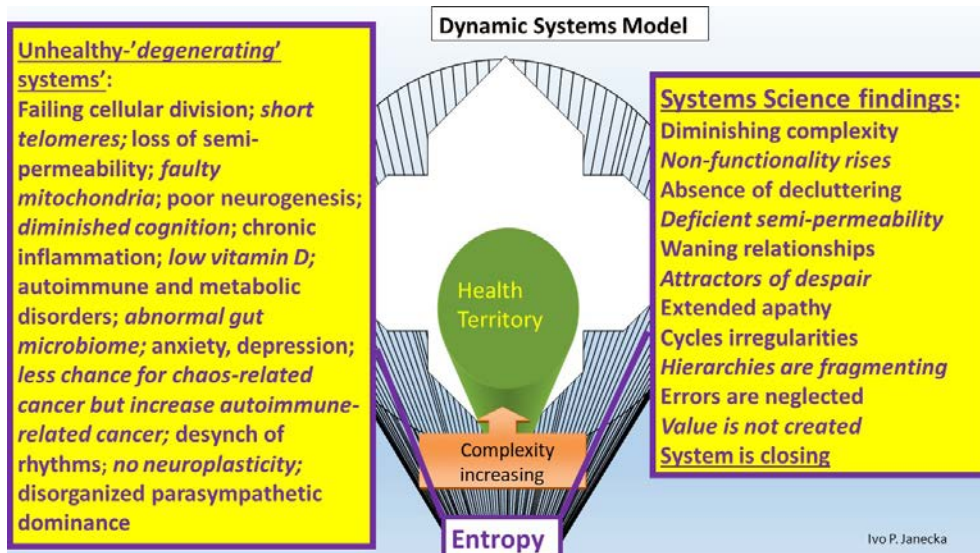


Figure 1d. Characteristics of biologic systems when in entropy - a 'degenerating life'

## 5. Terminology

**Awareness** - a state that can activate senses; attractors - what is chosen from awareness.

**Biologic time** - a cycle extending from its evolution-intended beginning to its natural completion, reaching progression-intended goals (e.g. multiplication, differentiation, repair and regeneration, recycling, etc.), regardless of what chronologic time happens to be; on one hand, chaos is conceptualized as a state of a biologic system, which does not complete its native cycle, such as inability to reach differentiation following multiplication, making such a system subject to a 'butterfly effect', a 'tipping point' of sudden decompensation into a 'cancer system'; on the other hand, entropy represents ongoing accumulation of non-functionality, leading to chronic inflammation with prominence of dysregulation of the immune system, creating a 'degenerating system'.

**Fitness** - combines endurance, speed, strength and flexibility.

**Hierarchies: Vertical** that 'govern' and **horizontal**

that 'does the work'.

**Healthy vertical governing hierarchy**, exercises 'macro-prudential' influence: good judgment with their laws, rules, and regulations in order to protect and provide safety with security for the whole system without exercising downstream 'micromanagement' of horizontal hierarchy.

**Healthy horizontal working hierarchy** has the capacity to create value if self-organization is permitted.

**Intelligence** - ability to solve problems preciously not encountered, based on a core knowledge of basic sciences, with the capacity for rationality and responsibility.

**Optimized** - capacity for generating health as value. Optimization is an evolutionary principle that preferentially seeks efficacy in its selection of function and structure; such a process minimizes energy expenditure, utilizes the smallest amount of storage space for its memory and assures subsequent correct translation of such memory.

**Relationship** - is healthy when expresses an aggregate of reciprocity, fairness, empathy, and trust.

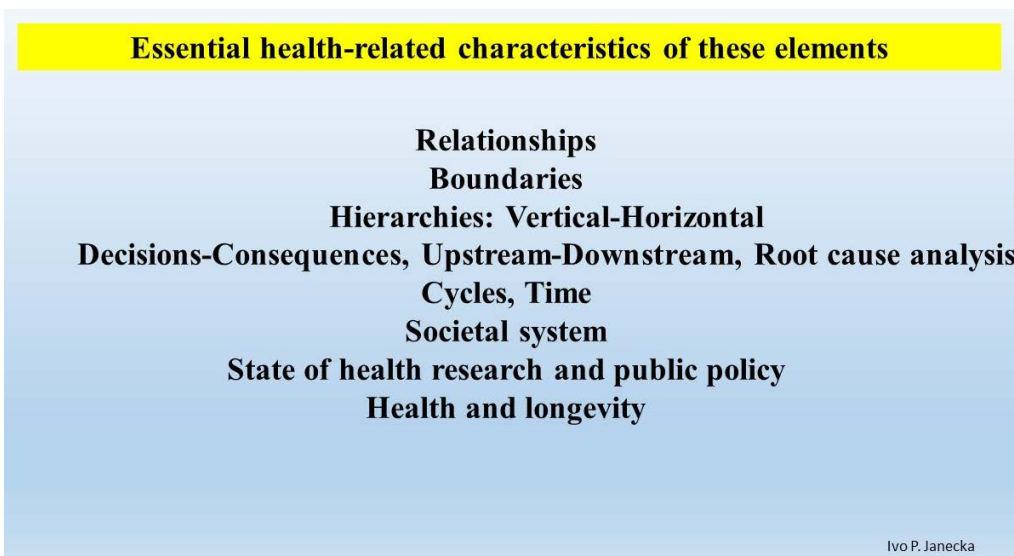
**Value** - an aggregate of efficiency, effectiveness, risk management and proportionate cost.

## 6. Discussion

Key functional and structural elements of a biologic system that directly impact health and longevity, have the following essential health-related characteristics: [Figure 2a,b]



**Figure 2a.** Functional and structural elements of a biologic system that directly impact health and longevity



**Figure 2b.** Essential health-related characteristics of elements in a biologic system

### 6.1. Energy and Mitochondria

Energy management is a common denominator of both physical and cognitive health status. For any biologic system to sustain its health, the intake-metabolism-output sequence must be in balance for both energy and cognition; the food-energy cascade begins with oral consumption that initiate metabolism, and the sensory input/intake begins with activation of receptors; both pathways have thresholds that are often massively oversaturated, resulting in distortions of metabolism and perception, damaging mitochondria and synapses; interval training, discussed below, encompasses physical fitness workouts and restriction of caloric and sensory input, a tripartite path that protect both metabolism and cognition.

All living cells require energy, generated by mitochondria, gifted by bacteria at life's 'beginning' of symbiotic

relationship with cells; throughout evolution, mitochondria have continued to be inherited but only through mothers, in the form of 'mitochondrial DNA' (mtDNA) on the X chromosome; females have two functional copies (XX) but males have only one (XY); when X is damaged in males, the remaining Y chromosome is not capable to restore it, shortening lifespan.

It is mitochondria that trigger senescence; the process begins with clusters of chromatin DNA and protein leaking out into cytoplasm, through deficient nuclear boundary, triggering inflammation. Currently, it is estimated that approximately 80 percent of older adults, those in the third phase of life (50+ years), have at least two chronic diseases, initiated mostly with unhealthy decisions that had damaged mitochondria, during the second phase of life (25-50 years); indeed, it may take 20+years from bad decisions altering epigenome to unhealthy morphology.

Functional integrity of mitochondrial membranous boundary, its semi-permeability, is essential for cells to be healthy; damage to the membrane is known to affect lifespan and plays a role in cancer, diabetes, neurodegeneration and in the ischemia-reperfusion injury. [7]

Healthy life uses 'clean', 'non-polluting', energy inputs, a bio-fuel, for mitochondria, as well as optimizing sensory input, an 'intelli-fuel, for cognition; if either or both are mismanaged, any remaining life is unhealthy and foreshortened.

When mitochondria are fed unhealthy diet, a 'contaminated biofuel', lysosomes, the intracellular recycling organelles malfunction, leading to an increase in cellular non-functionality, an entropy; as a consequence, cell membrane's semi-permeability is damaged. [8]

Vigorous mitochondria generate 'clean' energy for cells from a healthy diet, an indication of optimized nuclear DNA; by comparison, a metabolic syndrome, a consequence of unhealthy metabolism, poses a foundational risk to DNA and the entire biologic system. On a societal level, obesity-induced metabolic syndrome affects nearly 30 percent of the U.S. population, and increases the risk for type 2 diabetes, heart disease and stroke.

Metabolism is affected by volume, timing, and quality of what people eat as well as the quality and duration of sleep; each component has an optimizing range with a given threshold. Similarly to the relationship of food intake and the level of metabolic health, cognition, the perception-generating neuro-net, is impacted by what and how much is processed by senses with a strict threshold, in order to allow any eventual perception. Akin to the perceptual cognitive threshold, the anatomic neuro-net itself has a processing threshold, tied to a level of available energy from mitochondria, also with a threshold; indiscriminate sensory processing, diminishes the pool of available energy for sensory processing; if exhausted, it creates the likelihood of missing even critical signals.

Circadian rhythm of day-night oscillations affects mitochondria; if the circadian clock is impaired, so will the cycle of mitochondrial fission-fusion dynamics, causing a decline in energy production in the cells. [9] [Figure 3]

The functional integrity of suprachiasmatic nuclei, the center of circadian rhythm, is govern by the

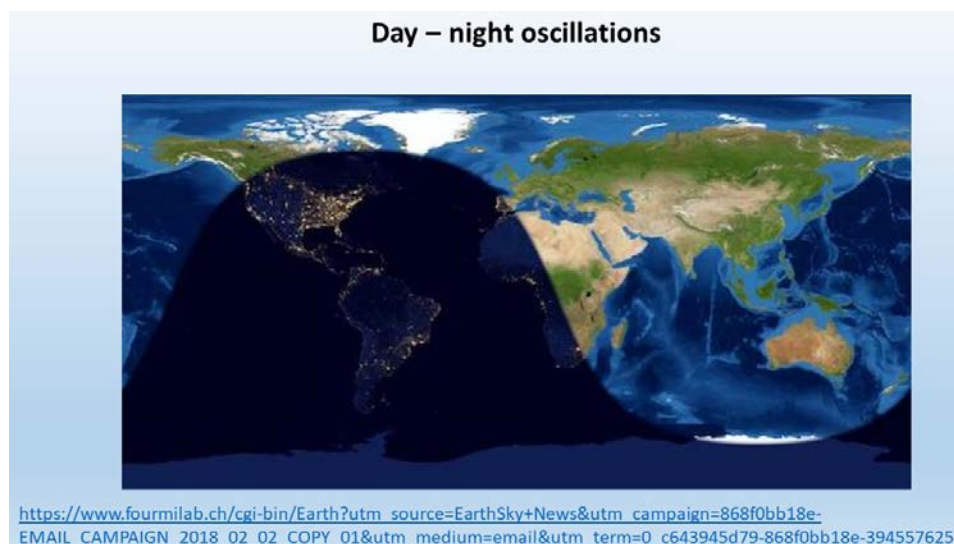
calcium-regulated potassium channels, TRESK, within their healthy boundary; they are active only during daylight; deficiency of membrane channels disrupts circadian oscillations.

Recycling and decluttering are both part of a healthy metabolism that reuses some components and discards others thus preventing entropy. Recycling, like most biologic processes, is a two-way street; in health, recycling has its confines and is beneficial; outside of health territory, however, in chaos or entropy, unhealthy/cancer cells may start recycling good cells. Lysosomes provide the venue for intracellular recycling and, correspondingly, communicate with mitochondria regarding their on/off status. Failure of decluttering, on all levels of living systems, is toxic to still healthy cells and generate chronic inflammation, a state of entropy, characterizing degenerative diseases, e.g. a failure of insulin production in diabetic patients.

Obesity is detrimental to all living systems and indicate malfunctioning metabolism; its negative impact on health is worse than smoking and includes the following: compromised genome with shortened telomere, weakened immune system, decreased cognition, likelihood of developing type 2 diabetes, hypertension, stress, Alzheimer's and cardiovascular diseases, cancer, etc., all entropy states; the key cellular failure comes from an overwhelmed recycling process. [10]

## 6.2. Brain and Muscle

'Movement and intensity', key characteristics of the Universe, are imprinted on life as existential requirements and health is simply part of the protocol; the triggers and executions of these two features are in the domain of 'muscles and brain'; both show great similarity in response to training: high oxygen and energy consumption, reliance on nutrition, cardiovascular fitness as well as 'active rest and recycling/decluttering'. Fitness follows training of different muscle groups to reach a balanced state; similarly, various brain regions must also undergo targeted training of input-output, e.g. linguistics, sensory, logic and art, etc., reaching a combined 'cardio-vascular-cognitive fitness'. [11]



**Figure 3.** Global day-night oscillations

Both oxygen and glucose/carbs are most needed in the capillaries of the vascular system, in order to assure peripheral tissue perfusion; on one hand, aerobic fitness maximizes this requirement, on the other hand, hypoxia has an unhealthy, multi-prong effect on tissues, threatening its survival and facilitate change of non-significant, differentiated cancer cells already present, into highly malignant cancer stem cells.

Both muscles and cognition have input and output limits, thresholds, which play a key role in performance; higher threshold offers greater physical and cognitive reserve; oversaturated one does the opposite. Interval aerobic training increases lactic threshold, causing an expansion of muscle capacity that allow greater and better performance through better oxygen utilization and efficient glucose metabolism; similarly, interval training with restriction of food and sensory intake, expands metabolic/mitochondrial and cognitive reserve capacity; to wit: synchronization of the medial and lateral prefrontal cortex allows differentiation of sensory input from data into knowledge; caloric restriction signals cells not to grow but to renew through recycling. Interval training schedule can accomplish better physical performance, better comprehension, and better metabolism.

Neuro-muscular junction is the translating boundary between nerve fibers carrying signals and muscle function; such junctions are distributed throughout muscles, but their higher density is based upon training; as the greater the fitness, the higher the number of junctions, as they develop along smaller and smaller-sized fascicles, offering higher and more specific muscular performance; without training, one junction is sufficient for many fascicles limiting function.

Declining motor function and increased frailty is an outcome of vanishing neuro-muscular synaptic endplates, primarily from disuse; to a limited extent, recovery can come from interval training.

Healthy anatomic neuro-net is evolutionary programmed, for what it considers optimal traffic of neuronal transmission, by keeping neurons alive longer than other cells, through diminished recycling via apoptosis; with never-ending indiscriminate traffic, however, capacity for apoptosis is likely exhausted and degeneration follows.

### 6.3. Cognition, Decisions, Perceptual Reality

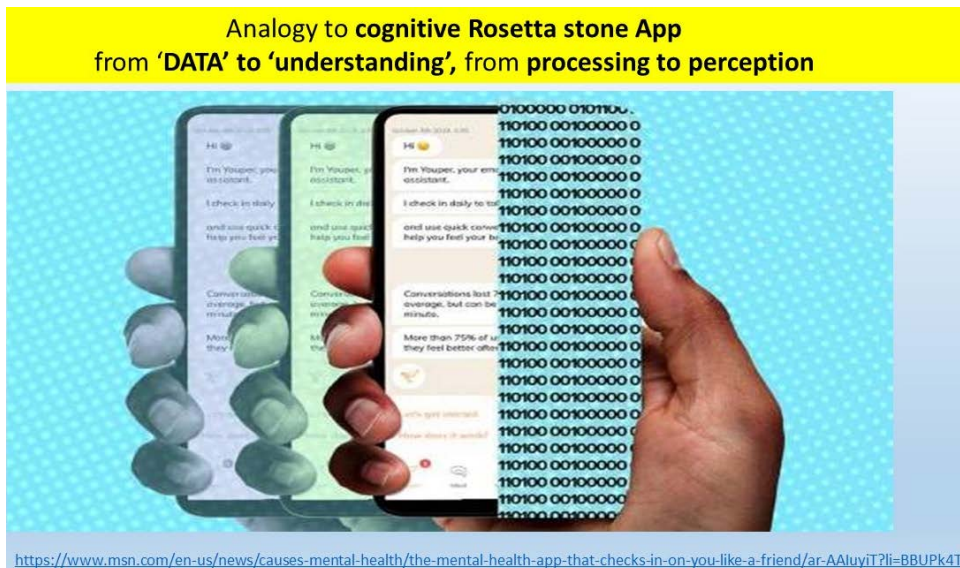
Biologic systems experience life with movement and intensity, repair, regeneration and reproduction, sensory awareness with attractor selection, input processing, perception and decisions; all this is allowed by a level of available consciousness, variable due to the degree of synaptic coherence; life-experience tasks require translation of any autonomic coding of ionic electro-chemical processing signals into the language of words, the inner silent thoughts of the mind, allowing eventual comprehension. A perceptual reality forms/constructs individual's concept of the world, but that can only extend within the boundaries of an operational 'language capacity' that translate the newly-received sensory input. [12]

Perceptual reality determines what is extracted, as attractors, from the next awareness of change that trigger senses; it influences how we understand/perceive the input and frame the 'next outlook'. How the perceptual reality

of an individual handles change is a reflection of its relationship with self and others. The initial encounter with change represents 100 percent uncertainty; once fully processed by senses, uncertainty can be differentiated into a quantifiable risk probability, offering a degree of rational optimism, and any remaining, but further not quantifiable uncertainty of randomness; the more risk is quantified from uncertainty, e.g. with technology-expanded senses, the less fear exists; subsequent decisions reflect those odds; risk, in this context, represents probability, not a random guess; persistent and dominant uncertainty generates chronic stress that is detrimental to system's boundaries, specifically to their semi-permeability; if affected, any subsequent decisions are negatively impacted; in addition, unfocused and overwhelmed cognition is unable to exercise any meaningful noise/signal reduction and distinguish, for example, health-relevant vs. irrelevant information, making decisions that are unclear and shrouded in rationalization.

Language is a gate to understanding and creativity, comprehension of self and the world around; some languages are based on 26 letters of the alphabet/symbols that are used in multiple combinations, offering the richness of a tongue; by comparison, a software language, so far, is using only two symbols, zero and one sequence, offering long lines of codes but not semantic richness; surpassing all languages, however, is the genome that have an option to use 20,000 exons of DNA code and the previously labeled 'junk DNA', representing the vastness of functional RNA; together, they offer an astronomical number of combinatorial options awaiting to be expressed; biologic adaptation and evolution has much to choose from. Learning the language of life, the ultimate and inexhaustible contextual/relationship communication format, is essential in order to advance intelligence of any living entity.

What we see is not what our senses record; it is what our cognition interprets as perception/understanding; following activation of senses, signal processing carries only electro-chemical signals in +/- code. The translation of sensory codes into words of the mind remains unexplained; as a conceptual metaphor, it can be called the Rosetta Stone App, developed through education, from home-to school-to life; of course, this language is the same one, which is being used for communication with others; the quality/character of translation of signals into words, however, depends on the type of language that is being used, with its rules, in order to reach any meaning. Is the boundary, its grammar, rigid with rules defining the meaning to the last option, or is there a greater porosity, semi-permeability, among the boundary of rules, allowing cognition to determine the comprehensiveness of the actual meaning? The latter language utilizes contextuality, arriving at meaning from cognition-revealed relationships; on a societal level, dominant use of such a language would likely lead to a greater capacity for inventiveness/ingenuity/intellect rather than a language that utilize rigid rules for formation of thoughts; indeed, some languages have so many rules that they leave almost nothing to the imagination, circumventing the influence of the vertical upstream hierarchy of cognition and force the user to go directly to the horizontal downstream hierarchy for meaning, controlled by inexhaustible rules of a given language; innovative thoughts emerge in the gaps of language rules, representing the role for cognitive vertical hierarchy. [Figure 4]



**Figure 4.** Rosetta stone app analogy-data translated into words

The still-conceptual Rosetta Stone App functions bi-directionally in order to re-translate thoughts back, from the 'language of the mind', into the electro-chemical signals that carry decisions; this step is done via distal processing to the end-organs, for example, the neuro-muscular junctions, in order to implement movement. Multiple translations among any languages, always carry the likelihood of various errors, such as inaccuracies of chosen vernacular and mistakes of understanding with miscalculations of decisions. Level of intelligence, related to an educational attainment and clarity of cognition, are essential to minimize errors, affecting the size of cognitive reserve, 3-D hippocampal memory, hypothalamic hormonal balance, cardio-pulmonary fitness, simply a state of health of a biologic system.

Biologic systems create errors, starting during selection of attractors from sensory awareness, to processing, perception, etc.; the big difference among systems is that healthy ones correct most errors quickly but such errors linger in unhealthy systems and create cellular stress; this distinction affects cellular multiplication-differentiation sequences with an increase in malignant transformation. Stressful life events contribute to worsening of existing co-morbidities; by comparison, healthy people, in spite of such events, usually continue to be healthy or quickly regain the state of health.

Healthy behavior must be established early in life and continue through the adulthood, the decision phase of life, in order to have a healthy biologic momentum going into extended life; interval training is the path; lack of morbidities is an acknowledgment of a lifelong affair with health that has focused on protecting mitochondria and cognitive competence.

Declining cognition, measured by impaired memory and loss of cerebral volume, follows long-term stress with chronically elevated serum cortisol; it is often generated by fear from unresolved uncertainty, lack of safety/security, poor sleep, etc.

#### 6.4. Interval Training (IT)

All living systems, large and small, have the capacity to respond to training, including cognition, the immune

system as well as gut and the epigenome. The foundation of any biologic system's health is 'training', involving all its subsystems (cardiovascular and pulmonary, cognitive, immune, etc.); these drills need to be frequent and intense, with up limit of physical fitness and selective limit for sensory and food intake; timing of each has to respect the specific cycle topology.

There exists a linear relationship between fitness and longevity and it seems to be without any weekly limit on the time that is devoted to training; the longevity benefit from training apparently does reach a threshold at a level 3-5 times higher (450-750 minutes/week) than the minimum public health recommendations; and, even at levels over 10 times higher, there is no apparent adverse outcome; as a consequence of such training, all-cause mortality is reduced by almost 40 percent. [13]

Interval training is efficacious; it provides significant enough 'change' to a living system that induce its adaptation and evolution, graphically pointing to the junctional margin of the health territory and chaos within the dynamic systems model; this is where muscles undergo hyperplasia and hypertrophy and 'brain-on-interval training' expresses neurogenesis with synaptic activation in hippocampus. [Figure 1a]

Aerobic exercise improves memory function and maintains healthy hippocampus (especially the left one), as increasing exercise generates greater amount of brain-derived neurotrophic factor (BNF) that offer neuroprotection and synaptic plasticity; there is an established link between aerobic exercise and better academic performance; in general, hippocampus shrinks about five percent per decade after the age of 40. [14]

IT, in an aggregate, encompasses high intensity aerobic exercise, caloric and sensory input restriction, which improves neurogenesis-inducing learning. IT increases multiple thresholds, and thus the reserve capacity of each subsystem (muscles, immune system, mitochondria, cognition, etc.); in addition, it maintains the balance between sympathetic and parasympathetic autonomic nervous systems, so essential for optimizing stem cells, the 'alfa and omega' of morphogenesis in repair and regeneration.

IT promotes upregulation of healthy genes and simultaneous downregulation of non-contributory ones, thus decreasing the overall number of active genes on intracellular histone proteins, only to those favoring health and longer life; in humans, such a process creates a functional epigenome and is primarily regulated by decisions/lifestyle choices that either increase or decrease the number of activated genes responding to our choices; all activated genes, however, have to be measured against a specific and finite threshold needed for cellular health; overcrowding, with excess of activated genes, leads to oxidative stress, inflammation, and accelerated emergence of 'aging diseases'.

IT improves cellular recycling, through hormonal signaling, by activated ubiquitin-proteasome pathway that tag misfolded proteins, implicated in neuro-degeneration.

IT generates short-term but beneficial stress during aerobic training, due to a sudden but temporary increase in energy demand; that leads to remodeling of mitochondria and the production of beneficial antioxidants; such a state protects cells and delays risk for diseases; a low and temporary stress signal of IT profoundly resets lifespan: for example, in laboratory experiments with *C. elegans*, these signals are thought to be interpreted by the organism as a way to reset itself and to live longer.

IT, through its moderate and temporary stress, has the ability to 'rewrite' the epigenome; such a capacity was first conceptualized by Lamarck in 1809. [15]

Physical activity is driven by cognition and its decisions; the level of physical fitness reflects the amount of cognitive focus transferred to muscle memory; the more you train, the more is transferred, an ongoing feed-back loop.

IT with intermittent fasting, caloric restriction (CR), is highly beneficial to health; it increases desirable heart rate variability by enhancing parasympathetic tone and reducing sympathetic one and with reduced salt load, it is reducing vascular resistance; balanced sympathetic and parasympathetic autonomic systems, are key factors in stem cells' health. deCabo and colleagues point out that fasting as training, can trigger a metabolic energy switch from glucose (originating in liver) to ketones (derived from adipose cells as fatty acids and ketone bodies); such a process increases stress resistance and longevity; it also decreases inflammation and free radicals, leading to reduction of cancer and obesity (with related metabolic syndrome); ketone bodies regulate the beneficial expression of, and the longevity-related, fibroblast growth factor, nicotinamide adenine dinucleotide (NAD<sup>+</sup>), sirtuins genes, etc. Furthermore, such training stimulates the expression of previously-mentioned brain-derived neurotrophic factor, benefits general homeostasis and adaptive stress response that lead to DNA repair, mitochondrial biogenesis and autophagy/recycling; it also enhances gamma-amino-butyric acid, an inhibitory neurotransmitter, which offers protection of synaptic thresholds. [16]

CR signals cell not to grow but to focus on cellular decluttering/recycling, allowing cells to renew; starting IT early in life, offers the greatest health benefit by reducing the probability of chronic cellular inflammation.

CR can offer protection to cells from an 'aging processes'; among experimental animals, over 50 percent

of the usually observed cellular changes with regular diet, were not seen with caloric restriction, such as the expected rise in immune cells and inflammatory markers in various organs.

CR lowers chronic, metabolism-induced inflammation and thus 'dials down'/modulates the long-term activity level of innate immunity; both factors have a positive impact on longevity. [17]

CR enhances the production of metabolites with antioxidants properties, a key factor in health and longevity; it also protects neuromuscular junction. [18]

Cognitive interval training (CIT), through intentionally and selectively limiting sensory input, frees-up a number of synaptic receptors, which expand cognitive reserve and protects cognitive threshold (similar to a healthy threshold limit for the number of activated genes, increasing the genetic reserve of the epigenome); CIT facilitates better oxygen utilization, efficient glucose metabolism, and synchronization of the medial and lateral prefrontal cortex, leading to better capacity to differentiate sensory input data into knowledge (again, a process similar to the ability of healthy life to activate genes only up to the epigenetic threshold).

## 6.5. The Connecting Script

### 6.5.1. Relationships

All living entities exist within inter- and intra-systems' relationships; there is no isolated, individual life; an output of one system becomes an input for others and *vice versa*.

Such a complex multidimensional relationship implies that even one malfunctioning/unhealthy small system, can negatively affect the function and structure of its larger system and so on; for example, healthy human decisions, the cognitive emergence/output of a biologic system, are formulated only when the synaptic neuro-net receives sufficient amount of correct neuro-transmitters, manufactured by healthy gut microbiome, which must have dietary fiber for energy generation; poor diet leads to unhealthy microbiome that fail to provide healthy neurotransmitters leading to subpar neuro-net and consequential non-optimizing decisions.

Several key components of a living system play a significant relationship role in its health or disease; they are: boundary and intake-throughput/metabolism-output sequence (with recycling/decluttering). A healthy boundary must be semi-permeable and intake-metabolism-output arrangement is to be proportionate.

Cycles are a form of relationships; many cycles are well known, such as day-night, birth-death; others, though essential for life, are not generally recognized as such; for example, not only the metabolic and cognitive cycles but also stem cells sequence from undifferentiated to a differentiated state; each cycle has a beginning and an end; some have numerous repetitions, others just one run; each, however, has the need to run its course in order to contribute to system's health; if a cycle is interrupted, unhealthy consequences ensue, e.g. interrupted sleep leads to subsequent cognitive underperformance or incomplete spermatogenesis, leading to poor quality of sperm, with a consequential impact on fetus.



Incomplete biologic cycles lead to greater susceptibility of recurrent infections, autoimmune diseases, diabetic heart and kidney disease, asthma, chronic obstructive pulmonary disease, Alzheimer's dementia, cancer and autism spectrum disorder, etc., all entropy events; during such chronic diseases, cellular boundaries harden leading to cascading effects with impairment of semi-permeability, diminished inter-cellular communication and the production of abnormal energy molecule ATP (adenosine tri-phosphate) by mitochondria, all demonstrating that cells are still within an unresolved cycle.

Sleep cycle readies synapses of the neuro-net for learning, by weakening them during sleep, in order for them to be strengthened with learning during day-time.

A cycle follows a course that has one phase of progression, with an increase in complexity, and another phase of regression that show diminishing complexity in healthy systems but increasing 'complicatedness' in unhealthy ones, expressed as degeneration in biologic systems; for example, embryogenesis propagates in complexity into a specific phenotype, while aging with morbidities regresses into degeneration.

In order to optimize larger systems, all cycles must be in synch with one another, within the topology of a specific hierarchical structure; specifically, the subservient metabolic cycle, initiated with food intake, needs to be in synch with the critical, and higher-order, day-night circadian oscillation; the pro-health timing for intake is to take place during daylight, which initiates digestion and starts the metabolic cycle; the restriction to daytime intake only allows for completion of food processing during night time. Similarly, a cognitive intake cycle should have sensory acquisition during daytime; night time should be reserved for cognitive decluttering/recycling/pruning of the synaptic neuro-net filled with daytime input; this pruning forms a foundation for subsequent optimizing decisions.

The function and structure of a human biologic system is evolving throughout three stages of its living cycle, averaging about 75 years, divided broadly into three 25 year periods: first is the ancestral phase, where a pre-set epigenome, by previous generations and shared through reproduction, is now operational in an offspring; as life continues in the second phase of life, the decision phase, the now-adult offspring, through own decisions, can modify its epigenome, which again can be shared through reproduction with a new generation, for a transgenerational influence; the last, third phase of life, the phase of consequences, primarily carries the momentum of previously set decisions-regulated epigenome with all its accumulated health or disease memory.

Almost 50 percent of adults die during the transition from second to third phase of life (45-65 years) due to multiple accumulated morbidities. [19]

The longest enduring and most significant relationship that humans have had, has been not with Lucy, the *Australopithecus afarensis*, or even the proverbial 'Adam and Eve', but with bacteria that, via endosymbiosis, apparently gave origin to multinucleated structures, currently known as mitochondria.

Gut bacteria, the microbiome, are the source of neurotransmitters for brain's synaptic net, transported from the gut to the central nervous system via the vagus

nerve. The long gut-brain connection has only one synapse, allowing a transmission signal speed under 100 milliseconds; many entropy diseases are thought to be triggered in the gut: obesity, arthritis, depression, autoimmunity, etc. [20]

The 'sharing' of bacteria continues to this day through transgenerational and multi-species transfers. It is known from human studies that mothers establish newborns' microbiome through the transfer of their microbiome that is present in breast milk, during breastfeeding, and during vaginal deliveries of their children. The third observation, still to be fully documented but suspected from the above observations, is that cows' milk is likely transferring cows' microbiome with hormones and antibiotics to people who drink such milk; the relationship between consuming cows' milk and breast cancer has already been reported.

Literature indicates that animals (gorillas, chimpanzees) that live in human proximity adapt human microbiome from their caretakers. [21]

It is the proximity of relationships among biologic systems that lead to similarities of diseases; e.g. wives of men with major cardiovascular disease risk factors, namely hypertension, diabetes, etc., often develop the same disease.

Gut microbiome is an active communicator with host's DNA via nitric oxide as part of epigenetic influence, broadly implicated in entropy diseases such as Alzheimer's, Parkinson's, asthma, diabetes, heart disease, and cancer.

Evolution favors healthy microbiome in symbiosis with a healthy biologic system; evolution delegates pathogenic microorganisms to a process of decomposition/decaying and recycling of biologic entities; when such microorganisms are found in a biologic organism, it indicates its failing health with multiple co-morbidities.

Microbiome is a component of the internal boundary; dysbiosis, an unhealthy microbiome, promotes/facilitates/allows acquisition of infections to the detriment of a living system. [22]

### 6.5.2. Boundaries

A boundary represents a margin, a junction, between a system and its environments; it intermediates many of its relationships, including alerting the immune system about pathogen transgression; based on its level of optimization, a boundary participates in 'what gets in', 'what goes out', and 'what gets recycled', including what you eat, drink, hear or see, and have relationships with, as well as what is recycled or eliminated; healthy systems have semi-permeable boundary with selective and tightly controlled porosity; a living biologic system has boundaries with physical, mostly continuous, properties, such as skin, mucous membranes, blood-brain barrier, etc., and also boundaries with cellular properties that are discontinuous but are acting in unison; e.g. the immune system, microbiomes, etc.; both types of boundaries, the physical and cellular, need to reflect systems science principle of optimization through tailored adaptation and evolution with change, for the benefit of the whole system; there are gaps in the continuity of the physical boundary (mouth, nose, etc.), where the selective permeability, the permissibility of transgression, is govern by cognition, human decisions; for example, a decision-induced inappropriate intake

corrupts metabolism with ongoing accumulation of toxic byproducts (e.g. misfolded proteins, Tau, beta amyloid, etc.), which are present in neurodegeneration.

Evolution developed boundaries to sustain life and it is up to all living systems to support them; from planetary boundary, the atmosphere, to individual physical and cellular boundaries, in order to allow life to go through its cycles.

Semi-permeability, the degree of dynamic porosity of boundaries, maintains systems' relationships, within a certain range among healthy system; boundary cannot be 'closed' or be 'too porous/leaky' as both options are unhealthy.

A boundary has many forms in living systems, but they all follow their evolutionary memory to sustain life; in humans, however, cognitive choices exist in terms of what to 'let in' the body & mind (food, information, etc.) and what to 'let out' (type of decisions, what to discard, etc.) that determine the degree of semi-permeability, which closely relates to the level of health.

A healthy boundary demonstrates its intelligent and dynamic semi-permeability, in terms of how it handles any exchange between external and internal milieu. For example, an optimized boundary of cells depends on saturated fatty acids but only short- and medium-chain length; consuming diet with mostly long-chain fatty acids, the normally flexible boundary, becomes rigid.

Furthermore, decisions to consume unhealthy food by pregnant mothers, weakens fetal immunity through placental transmission (upstream-downstream causative influence: mother's decisions leads to fetal consequence, a transgenerational impact).

Immune T-cells, part of the internal cellular boundary, have variable response repertoire, based on previous experience that created system's memory; at birth, the initial endowment of immunity has only 'naïve' T-cells; each subsequent encounter with pathogens, either from the environment or via live vaccination, is added to such memory. [23]

Innovation, a search for optimizing principles of biologic systems, requires: one-selective porosity/semi-permeability of all boundaries, and two-optimizing relationship between vertical and horizontal hierarchy (see below); these two foundational dependencies are quite visible on a societal system level, where, for example, 'totalitarianism' of the vertical governing hierarchy, stifles self-organization, essential for innovation, within the horizontal working hierarchy; similarly, in a single individual, decisions, representing vertical hierarchy that are attempting to control cells and their organelles within the horizontal

hierarchy, damage their innovative capacity for adaptation and evolution, which is key to a healthy continuum of life.

### 6.5.3. Hierarchies

#### Vertical-Horizontal / Upstream-Downstream

The COVID-19 pandemic of 2020 demonstrates that the 'virus', a downstream illness, takes a secondary role to the massively unhealthy global societies, the upstream etiology, with immune dysregulation of cellular boundaries; the vast majority of deaths have been among patients with multiple morbidities.

The negative impact of non-optimized immune systems, representing the cellular boundaries of biologic systems, has increased in the last few decades; for example, the prevalence of antinuclear antibodies, though not a 100 percent accurate test but valid for comparison with other timeframes, is now approaching about 16 percent of the population; those antibodies often herald autoimmune diseases, an unhealthy entropy system state. [24]

High intake of dietary salt, over 5 grams per day, increases the levels of glucocorticoids, generating a chronic immunosuppression through the inhibition of granulocytes.

A decline in physical fitness and immune system competency, are considered the key features of aging, accompanied by chronic, low-grade inflammation, an entropy state.

Learning loops exist in order for any vertical hierarchy to have the optional capacity to proactively and efficaciously help a system to adapt and evolve with conflict and uncertainty resolution; this learning function is not intended to exert control over the downstream hierarchy but to facilitate its self-organization. Among humans, the decisions-consequences learning loop often stretches over 20+ years, an evolutionary grace period, before the consequences catch up, when no learning had taken place, and morphology finally expresses diagnosable disease; looking at the smoking-lung cancer example, unhealthy choices negatively altered the epigenome during the phase two of life, the phase of decisions (from mid-twenties to mid-fifties); using this timeframe, fixing an unhealthy epigenome would likely take similar time, another 20+ years; unfortunately, the cycle of human life, for most, is currently ending in the mid-seventies and the option for healthy adaptation and evolution has run out of time; the critical time for optimizing, pro-health decisions, is with 'every breath' you take, with every 'morsel' that you eat, throughout the entire life. [Figure 5a,b]

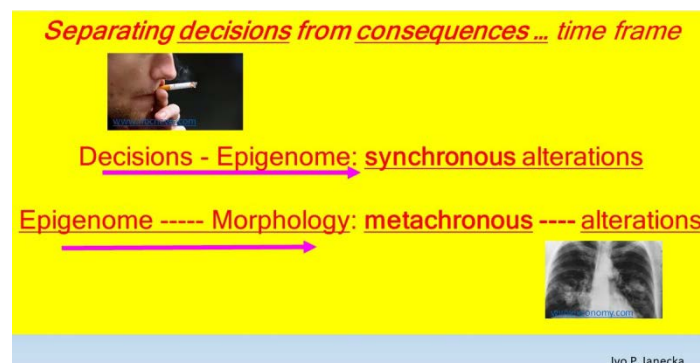
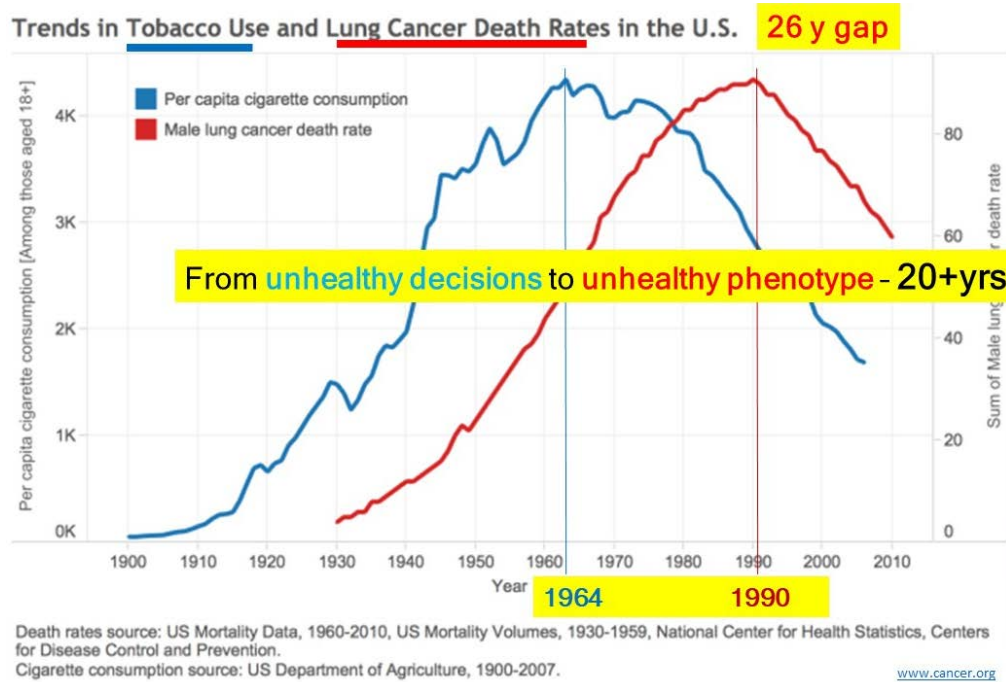


Figure 5a. Decisions-consequences-epigenome and morphology time relationships



**Figure 5b.** Time delay between decisions and consequences of smoking

During a healthy life, there is ongoing ‘learning through doing’, principally through proactive training that incorporate decisions-consequences loops within known cycles; even in the hippocampus, for example, new neurons are formed and, with new experiences, new memory is synchronized with brain oscillations, at synaptic levels, during REM sleep cycle.

Cognition is the vertical/governing/upstream hierarchy of a living system, and is responsible for: 1-safety and security of the entire biologic system and its innumerable smaller systems (organs, cells, etc.); 2-cognition must allow for self-organization, with the potential for value creation, by the horizontal/working/downstream hierarchy; it is counterproductive and unhealthy, for vertical hierarchy to control the horizontal hierarchy in its operational details (via funds, rules/regulations, etc.). On a societal level, if the vertical hierarchy (political or research) does exert total control over horizontal hierarchy, the hoped-for cures in health care are unlikely to materialize; this is because the revelation, of what significant remedies are, lies in the recognition to what the causative upstream etiology is; instead, the controlling vertical hierarchy, through renaming downstream goals for many researched cure into arbitrary surrogate markers or using different criteria for cure, will not produce the desired outcome, as all biologic cycles have to be allowed to run their course, in order to reveal any effectiveness of intervention, and only then, a judgement, regarding the validity of result, is appropriate.

**Decisions-consequences**

Most living entities have an evolution-assured direct link between their ‘decisions/choices/lifestyle’ and ‘consequences’; not so among humans, who have created large gaps between their ‘private’ decisions and ‘deferred’ consequences; ‘private’ decisions should be considered a misnomer as they are never ‘silent’ in their impact on the decision-makers’ epigenomes; decisions reflect the

intelligence of their source; a healthy one encompasses: 1) responsibility-for all related systems (e.g. sub-systems of self, such as organs, microbiome, etc. and large systems, such a society, Nature, etc.) , and 2) rationality-that is based on the current core knowledge of basic scientific principles (biology, chemistry, physics, math, etc.).

The medial frontal and lateral prefrontal cortices of the brain control most executive functions through synchronized oscillations that allow for focus, correction of errors (the medial cortex) and optimizing/healthy decisions with rules and action (the lateral cortex); in healthy individuals, synchronization is at low frequencies that have greater reach; by comparison, desynchronization occurs at higher frequencies with shorter reach and ‘louder’ amplitude, common in neuro-psychiatric diseases (anxiety, Parkinson’s and Alzheimer’s diseases, autism, schizophrenia, ADHD, and others). [25]

Decisions create the outcomes of living systems’ existence with variable quality and impact; healthy/optimizing decisions require focus, a singularity of dominance of cognition over a task; a pre-requisite, for optimizing/healthy decisions, is the existence of healthy/optimizing perceptual reality and the availability of an unsaturated cognitive threshold, with suppression of most of other relationships. Focus leads to a coherence within the chain of inter-connectedness among decisions, performance and consequences; decisions create downstream consequences that construct a decision-consequence learning loop, establishing upstream-downstream relationships and open the possibility for learned adaptation and evolution; however, in human societies, though well-intended, the trend has been to separate health-related decisions from consequences; unfortunately that continue to lead to more health care but not better societal health; such a trend finds a parallel in many research fields, with emphasis on disease presentations, downstream manifestations, far removed from the upstream, decisions-based, etiology; long-term health cannot be restored without addressing the upstream issues.

There is a lot of background processing, before a decision is made; broadly, it starts with a pre-set epigenome and perceptual reality, as well as levels/types of available hormonal and synaptic neuro-transmitters, etc., before a single thought emerges in the mind; there is no such thing as 'deciding on moment's notice'.

Cognition, through its decisions, affects the epigenome and immunity, both in a cause & effect manner, without judgement, only fulfilling cognitive instructions; all decisions, starting with the upstream directions of the vertical/governing hierarchy of biologic systems, are recorded in real-time and carried out by the epigenome as well as immunity, both part of the downstream horizontal/working hierarchy; the morphologic manifestations though are metachronous, making the connection between decisions and outcomes, if not anticipated, rarely acknowledged, often perceived as distant memory; however, the expression of 'mis-learned' immune memory can be 'faster and furious' through anaphylaxis/cytokine storm.

Human cognition can understand sensory input with a processing speed only up to about 60-110 megabits per second, a conversational speed; above that, the input vanishes into an 'abyss' without leaving any recorded memory. An oversaturated cognition, often with mostly non-significant information/input noise, can lead to disregarding even an obvious danger, as the information is not fully registered as critical by cognition; this leads to an irrational state of oblivion in the face of danger, seeming paralysis of decision capabilities and any needed proportionate response; simply, the critical information ended up in the email-familiar 'junk folder' of memory because the 'inbox' was full; even the clearest signals/warning may not be heeded.

### Root cause analysis

Upstream etiology is the most proximate cause of a given disease, its downstream consequence, e.g. a decision to smoke is an upstream cause, and lung cancer is the downstream consequence; screening for and treating lung cancer will not alter the upstream cause, which is intentional, decision-permitted, a transgression of oral boundary with cigarettes, etc. However, simultaneously applying systems science-based root cause analysis to each encountered disease, will reveal the short-term and long-term corrective steps needed for health recovery; this process is broadly analogous to the development of eddies vs. streaming of whitewater during rafting; avoiding the first, eddies, may save you from capsizing, joining the other, the whitewater, is the go-forward path.

### Cycle, Time

Sumerians (circa 4500 BC - 1900 BC), a city-state civilization in southern Mesopotamia, are credited with the establishment of arithmetic, geometry, and algebra, in addition to formulating time of day into hours still in use today as chronologic time. [26]

Fragmentation of sleep time contributes to chronic inflammation, evident in rise of the level of inflammatory white blood cells.

Melatonin, a hormone with anti-inflammatory and anti-oxidant properties, maintains efficacy of mitochondria and extends performance of skeletal muscles; it is produced

during dark hours of night, by the pineal gland in the brain, and, following food intake, in healthy gut.

Sexual and neuro-net maturity are key crests in life of biologic systems; they are intimately related but their peaks are offset by about 10 years; the peak of sexual maturity is at the start adolescence, the second, when adulthood begins; it is only in mid-twenties that cortical neurons reach their anatomic maturity in the prefrontal executive cortex, offering more solid base for making decisions that can modify the inherited epigenetic memories and form new ones as well; the staggered peaks, the reproductive-cognitive gap, has significance for transgenerational influence; for example, an unhealthy epigenome, inherited from parents, can be transferred to the next generation if teenagers' reproduction is initiated before cognitive neuronal maturity because the pre-set epigenome of parents goes with it; if reproduction takes place in the second, the decision phase of life, the impact on offspring depends on the current, hopefully healthier, level of epigenomic memory, and so on. Once a top of either crest is reached, a decline ensues and is clinically measurable in both hormones and cognition; it is also feasible, morphometrically, to compute the absolute number of neurons in the cerebral cortex, the framework for emergent cognition; when measured across worm-blooded species, this number can predict about 75 percent of all of the variations in longevity and sexual maturity, regardless of body size and across species; the basic correlation is that overall, having more neurons equals longer life, verified by evolution; as a consequence, what limits lifespan the most, is harming the neurons in the cerebral cortex, which are essential for successful adaptation and evolution, via cognitive choices and decisions; the reference number of neurons in the human brain averages 86 billion. [27]

In childhood, stress of trauma compresses the two biologic cycles: it speeds up the onset of hormonal maturation with an earlier arrival of puberty, and it also shortens biologic life cycle, causing early mortality; the consequences of childhood stress are visible throughout an affected biologic system, from thinning of cerebral cortex in areas that process social and emotional information, to shorter telomeres and the presence of aging patterns of methylation markers on epigenome; in adulthood, numerous morbidities are then likely to appear, e.g. cardiovascular disease, diabetes, cancer, etc. [28]

Circadian day-night oscillation, with inverse secretion cycle of melatonin, must be allowed to be dominant to the metabolic cycle: food intake, only during daytime, allowing metabolism to be completed during nighttime. Extending food intake into the nighttime, restarts the metabolic cycle and suppresses the circadian rhythm, with all of its receptors in every cell, a never-ending 'cellular jetlag'. It is estimated that for every hour of variability in time to bed and time asleep, a person may have up to a 27 percent greater chance of experiencing a metabolic disorders.

Biologic age reflects system's adaptation and evolution that continue without morbidities until its birth-death cycle is completed. Chronologic age simply records the accumulating morbidities superimposed on the number of day-night Earth's revolutions since birth; there is no causative relationship here, only an association.

Morbidities, such as obesity, hypertension, cardiovascular disease, Alzheimer's disease, etc., originate with non-optimizing decisions, mostly during adulthood, which are followed by metachronous disease manifestations. A person's age and thus 'age-related morbidities' are mostly outcomes of 'what you eat and how you sleep', consequences of decisions-induced epigenetic changes, a process of making unhealthy decisions but deferring the disease causes, consequences, to Earth's rotations.

Epigenetic changes, such as methylation patterns that are different from healthy people, have been already detected in pancreatic Langerhans cells several years prior to the clinical appearance of diabetes. [29]

Obesity and aging are in self-enhancing relationship: as obesity increases so will 'aging'; the negative consequences can be observed within multiple sub-systems: the genome-shortening of telomeres, cognitive and immune system regression and weakened recycling, with numerous diseases in evidence - diabetes, Alzheimer, cardiovascular, cancers, and many others. It is estimated that almost 2 billion people in the world are obese with about 400 million children whose spectrum of diseases is now same as in adults: chronic lung disease (mostly asthma), obesity, neurologic/developmental conditions, and cardiovascular conditions, etc. [30]

### Societal system

A society is a living system composed of individual members who have the role of sub-systems; as such, a society is subject to the same systems science principles offering a healthy or an unhealthy existence.

Current global societies reflect a massive shift away from health into an unhealthy state of entropy, with increasing accumulation of non-functionality and multiple morbidities; this observation indicates that many systems science principles have been violated by individuals, such as, loss of semi-permeability of boundaries, imbalance of intake-metabolism-output sequence, privatizing decisions but socializing consequences, loss of understanding how an upstream vertical/governing hierarchy must relate to a downstream horizontal/working hierarchy, etc.; all of these abnormalities result in disorganized complexity ('complicatedness') and loss of value creation by systems; entropy diseases are not far behind, such as obesity, neuro- and cardiovascular degeneration, autoimmune problems, etc., cumulatively joining the downward spiral of the entire system away from health; by comparison, the true 'super rich' are not those with financial wealth but those few in excellent health.

A society, where most of the population is unhealthy, with multiple co-morbidities, becomes very susceptible to large-scale ill-health from any etiology; unfortunately, such a society will not be able to make optimizing/healthy macro decisions in order to proactively resolve various pathologic micro-issues arising in ecology (e.g. viruses, floods, etc.).

In recent years, the rapid rise in obesity with metabolic syndrome and neurodegenerative diseases, when charted, showed the start of an exponential curve, which, in any area of human endeavor, (financial, infections, physics, mathematics, etc.), is a warning sign of a great negative significance; for a large social system, the above-mentioned entropy disease clusters are of existential importance.

Virulence of any pathogen is related to the host's level of health; the better its state, the smaller, inverted, is the risk of a serious illness; an unhealthy body allows microorganisms to achieve exponential growth and toxicity very quickly; in addition, aggregating many unhealthy hosts in close proximity, is what provides the final impetus, the 'knee' of an exponential growth curve of the pathogen with accompanying pandemic and panic. Healthy people/biologic systems, those in health territory of the dynamic systems model, have the capacity to correct errors quickly, e.g. short and mild illness, if a new pathogen, still unknown to an individual's immunity, is encountered. Government's control of downstream unhealthy societal decisions is not the long-term answer as people adjust/bypass the 'barriers to entry' and focus on some other unhealthy lifestyle choices (e.g. attempts to control consumption of alcohol, smoking, drugs, etc. has failed because people that are used to making unhealthy decisions, will simply focus on other unhealthy lifestyle choices). A well-known example: the downstream efforts to cure cancer, during the 50 years of 'War on Cancer', have remained elusive in spite of prolific scientific literature on the subject. [31]

The 2020 pandemic illustrates the relationship between an individual's state of health and societal susceptibility to infection; it is all in the prevalence; in spite of variable presentation and affliction of various societal groups by the COVID-19 virus, the pandemic did have a common denominator - multiple pre-existing co-morbidities among the most severely affected patients; unhealthy/non-optimized biologic systems turned out to be the most susceptible; and, the already staggering number continues to rise. Contrary to the logic of social distancing, quarantine, etc., such public policy fosters anxiety, psychosocial insecurity in unhealthy population and that lead to more obesity and further lowering of vitamin D levels; sequestering only unhealthy individuals would have been effective and sufficient.

Patients hospitalized with COVID-19 were over three times more likely to die if they had metabolic syndrome, a consequence of obesity.

Obesity (body-mass-index/BMI over 30) has been linked to higher risk for COVID-19 complications: increased risk for hospitalization (113 percent), higher probability of needing an intensive care (74 percent), and have a higher risk of death (48 percent). Obesity is already associated with hypertension, heart disease, type 2 diabetes, and chronic kidney and liver disease. Metabolic changes caused by obesity - such as insulin resistance and inflammation lead to unhealthy immune systems because the uncontrolled serum glucose impairs immune cell function; of concern is, per Popkin and others, that any vaccine will likely be less effective in adults with obesity, thus the majority of the population. [32]

In retrospect, the 2020 pandemic could provide the most dramatic example of the existence of global entropy, where, it seems to have been the dysfunctional human immunity boundary, among those who experienced the severe cytokine storm following the contact with COVID-19, often with fatal outcome; it was not the virus *per se*, as healthy people were mostly asymptomatic, even when tested positive; the fact that the majority of the global population is unhealthy, waiting for a generalized

societal 'herd immunity' seems counterintuitive; hence, only in predominantly healthy society, considering 'herd immunity' would make some sense, but that is not the state in 2020. Obesity, a prime example of an entropy disease, can claim the unfortunate credit for being an independent risk factor for severity and death from COVID-19 virus, where obesity, severity of disease, and mortality were in a linear and a mutual causative relationship.

Many entropy diseases have a dysfunctional natural killer cells (NKC) of the immune system; when healthy, NKC begin and end the beneficial cytokine production by T-cells, following encounter with a pathogen; patients with COVID-19 and severe rheumatic illnesses, for example, experience the cytokine storm because its production by T-cells is initiated but not shut off by unhealthy NKC, related to low vitamin D levels; aerobic fitness, however, boosts the NKC healthy activity. [33,34,35]

Epidemics, such as SARS, HIV, corona virus, etc., heighten societal attention to health, through mostly fear of the 'invisible', but those viral diseases usually kill a very small percentage of a healthy population; unfortunately, the largest ever epidemic, which is obesity, an 'oral intake overdose', currently affecting over 2 billion people worldwide, is mostly ignored as it is 'visible and ubiquitous' thus not generating fear; most obese individuals will eventually develop some form of metabolic syndrome with all its complications including heart-lung disease, cancer, diabetes, hypertension, neuro-degeneration, such as Alzheimer's disease, etc. and all end up with a shorter lifespan, which can be measured by the foreshortened telomere.

Centers for Disease Control (CDC) reported that nearly 90 percent of adult patients, hospitalized with COVID-19 in the US, had one or more underlying diseases, mostly outcomes of metabolic diseases: hypertension 49 percent, obesity 48 percent, chronic lung disease 34 percent, diabetes 28 percent, and cardiovascular disease 27 percent. These conditions were nearly 100 percent prevalent in deceased COVID-19 patients; U.S. obesity rate has now reached 42.4 percent and one in six children is obese; of note, regarding the success of treatment of preexisting diseases, only 1 in 4 of those affected, have their laboratory/test numbers under control; the statistics for children were similar. [36]

Further supporting the relationship of severe COVID-19 infection and immune system malfunction, is the observation of an overactive complement of the immune system in many patients who also had age-related macular degeneration, an autoimmune disease, which is known to express hyperactive complement; ordinarily, healthy immune complement marks pathogens for destruction and recycling; hyperactivity of the immune system is known to be present in obesity and diabetes, entropy diseases categorized by the dynamic systems model.

The impact of obesity on a biologic system is similar to the current concept of aging, as described by Tam and colleagues: compromised genomes, weakened immune systems, decreased cognition, increased chances of developing type 2 diabetes, Alzheimer's disease, cardiovascular disease, cancer and other illnesses; obese/overweight children now manifest many obesity-related diseases that used to be seen only in adults.

Humans are not keystone species on this planet, whose disappearance would have cascading and negative consequences on Nature; on the contrary, many observations during COVID-19 pandemic (2020) actually demonstrated a significant improvement of the environment with human distancing and lockdowns, significantly lessened pollution (air, acoustical, water, etc.).

CDC estimates that more than half of adults and one-third of children and teens in the United States live with at least one chronic illness.

### State of health research and public polity

Back in 2010, it was projected that the rate of obesity would dramatically increase into 2030; the chart was forming a knee of an exponential curve. With the majority of society in an unhealthy state, due to dysfunctional defenses of the immune system boundary, the message from the chart was that bacteria, viruses, etc. would soon become pathogens for the majority of the population; a potential for a global health crisis was 'in the charts' then and, in 2020, the COVID-19 appeared and infected the world.

The momentum of societal research and clinical focus continues to have a strong downstream concentration, leaving major gaps in investigating and correcting upstream etiologies, the most proximate reasons for downstream illnesses; public policy reflects such a narrow focus, detrimental to other parts of the larger system. For example, the use of the bisphosphonate alendronate for osteoporosis is associated with significantly increased risk of arrhythmia.

### Health and longevity

Health is not health care. Health is an emergence of value from self-organization of its components, subsystems (organs, cells, etc.), considered to be the biologic systems horizontal working hierarchy; the vertical governing hierarchy, with its cognition-generating decisions, needs to facilitate the process; in the absence of self-organization, no value is created and the deficiency of health is prevalent. Decisions carry the authority to implement innumerable downstream modifications of the epigenome; the impact is automatic and reflects the quality of the decisions; eventually, often after a period of years, these messages, translated/coded into protein synthesis, create fully visible morphogenesis, either healthy or not; ribosomes do the conversion when they interact with messenger RNAs (mRNAs), the blueprints for protein synthesis, decoding the nucleotide sequence of each mRNA into the amino-acid sequence of the corresponding protein.

Health care is a downstream business system, managing the care of human morbidities for a price. Health has to be earned and sustained as a life without morbidities; it cannot be purchased; longevity follows as a consequence of life-long health.

Health care has primary orientation toward treating ever-increasing downstream disease manifestations, morbidities; this is likely due to the fact that altering the causative upstream etiology, such as behavioral/lifestyle choices/decisions for most diseases, has been an intractable problem throughout history; an extreme example, recently invented wireless smart contact lenses

for diagnosis and treatment of diabetes, which is mostly an upstream-originating diseases, consequences of decisions regarding diet, exercise, etc.

The essence of health and longevity begins and ends with a single measure, the efficacy of living system's boundaries; most unhealthy systems have dysfunctional boundaries, stemming from lifestyle choices.

In spite of dominant societal perception, a genome has very limited influence on longevity; it is all up to the decisions-altered epigenome. For example, common gene mutations, single nucleotide polymorphisms (SNPs), have almost zero (less than 5 percent) correlation with most diseases with the possible exception of Crohn's disease, celiac disease, and macular degeneration. [37,38]

Statistics reveal an ever-increasing accumulation of co-morbidities during adult lives; each additional morbidity adds to the cumulative cellular stress, impacting the function and structure of living systems; a healthy life is far 'more than a sum', it is the value creation by downstream subsystems, but as an outflow of upstream optimizing decisions.

The 'life lived' can be estimated from the length of a telomere, the end-of-chromosome nucleotide sequence; this is of significance not only to the 'present owner' of the epigenome but also to subsequent generations because an encoded epigenome, through reproduction, is transgenerational.

Shortened telomeres, commonly found in cancers, reduce the activity of intracellular and longevity-related proteins, the sirtuins; when activated with interval training, telomeres can be renewed.

Epigenetic memory is simply a record of decisions, through activation or deactivation of various regions of genome, without actually changing their molecular structure; we all have the same genes but we critically differ by the pattern of epigenetic memory that utilize the process of methylation as well as replacement of histones with histone variants. This sequence is analogous to the difference between inputs, registered by senses that we all have, and our perception, the understanding of the inputs, which is purely individual.

Reprogramming an epigenome is possible with ongoing decisions and behaviors, through a process of demethylation; vitamin A and C facilitate such a change of cell identify, which must take place before new ones are created.

Lifespan can extend, from the current average life expectancy at birth of 72 years, to over 110 years; it is not possible to achieve it, however, without health, and health is not likely to be sustained without the cognitive capacity to resolve uncertainty and the protection of semi-permeability of boundaries; all the daily encounters with uncertainty, and the following decisions regarding lifestyle choices, cannot be successfully carried out without intelligence.

Intelligence represents cognitive potentialities of a biologic system, specifically its neuro-net; as such, it can never have a 'fixed measure' by which to judge it. While any definition of intelligence is never precise, it can, however, be directly correlated, (no, this is not a surrogate marker), with human decisions, categorized into two polar opposites: 1-healthy, and 2-unhealthy; with such a

tool, intelligence is either clearly visible (health) or not (indicating the presence of morbidities); one cannot focus on a definition of an abstract construct, in this case intelligence, while not taking into account the expressions of intelligence, human decisions; and, it is the decisions that matter the most to life and societies. Health is an emergence of a complex adaptive system, a human body, in form and function. Intelligence, the upstream cognitive process, can only be judged by its downstream consequences, as the potentialities now become realities; you cannot be judged to be 'intelligent', while harming self and/or others with unhealthy behavioral and lifestyle choices; deductive logic is too simplistic to be used to constrain intelligence, which simply represents 'factors considered' but not all those that were 'excluded'. A society reflects the prevalence of health or disease among its members, impacting the resulting collective intelligence, generating a corresponding level of rationality and responsibility, as a summation outcome of intellect levels of individuals within a societal/cultural cluster. Intelligence is needed for proactive adaptation and evolution, principally based on the most effective and tightly connected feedback learning loops between decisions and consequences; when present, such a biologic system is bi-directionally proactive, so that while making a decision, an immediate question is also asked and visualized: what is the downside?, always being aware that all decisions are simultaneously recorded in the memory of the epigenome and the consequences will eventually materialize. Of concern is the observed societal prevalence of cognitive decline over the past 20 years, (1996 to 2014). [39]

Life expectancy research, published in 2020, indicates that lifestyle choices, such as smoking, heavy alcohol use, unhealthy diet, and lack of exercise, are shortening lifespans for 30 year old men by about 20 years.

Adults with healthy lifestyle choices, regarding diet, exercise, and stress management, are likely to live over a decade longer with life expectancy for women to be 14 years longer, up to age 93; for men, healthy choices extend lifespan by about 12 years to age 88. [40]

U.S. life expectancy, however, stalled in 2011 and began a slow decline, hitting 78.9 years in 2016, mostly due to increases in mortality in midlife; major causes: fatal drug overdoses, alcoholic liver disease, suicide, and hypertensive disease, all decisions-induced.

Human life is not a pre-ordained karma with a pre-determined outcome; life is modifiable by individual decisions; consequences, however, are predictable based on preceding decisions; healthy life is optimizing, expressing proactive adaptation and evolution with longer life expectancy; an unhealthy life is devolving into various morbidities and is associated with shortened lifespan.

Adaptation and evolution processes of biologic systems are induced by changes in either external or internal environment that are significant enough to occur at the topologic 'margins of health territory' within the dynamic systems model, see again Figure1a; the well-known 'natural selection', is simply evolution following adaptation; it acts most strongly not during time of abundance but during times of stress and scarcity, offering another rational for the benefit of interval training, a form of reversible stress.

Twenty-five-year-long study of adults, aged 45 years and older, revealed that 9/10 individuals developed multiple morbidities during their lifetime.

Healthy longevity requires biologic systems to maintain highly functional semi-permeable boundaries, principally carried out by cognitive decisions and eloquent immune system; all other 'steps of living' of biologic systems (intake, metabolism, and output) are subservient to these fundamentals. In supercentenarians, the acquired immunity has been refined through life-long interval training of adaptation and evolution; observation of current general population, however, shows continuous engagement with chronic inflammations such as in obesity, etc. Healthy immunity, as a cellular boundary, not only defends against pathogens but also influences aberrant, but not clinically detectable/significant, tissue transformation into obvious cancer, due to failure of its recycling capacity.

In 2015, Japan had three times as many supercentenarian (110+ years) as the US: In Japan, there were 146 supercentenarians with population of 127 million, almost 1/1 million population; in US, there were 110 among population of 320 million, only 1/3 million. Researchers found that the Japanese supercentenarians were relatively immune to illnesses (infections and cancer) during their whole lifetimes; the supercentenarians had a very high level (four time more than normal) of cells that are cytotoxic, carrying on cellular decluttering/recycling, sometimes amounting to 80 percent of all T-cells, compared to just 10 or 20 percent in general population. Normally, T-cells (type CD8) are cytotoxic, and those with the CD4 marker are not; however, CD4-positive cells of the supercentenarians had acquired cytotoxic status, likely through a life-time of healthy epigenetic influence; by comparison, in the blood of young donors, there were relatively few CD4-positive cytotoxic cells, indicating that this was not a marker of youth but rather a special characteristic of the supercentenarians, who created their healthy epigenetic influence over phases of life. [41]

The New England Centenarian Study at Boston University, estimates that 70 percent of the aging process can be attributed to health-related behaviors; men are less likely to be affected by diseases, though women who live to extreme ages are more prevalent. [42]

The gut microbiota of extremely healthy elderly (no known health issues up to age 100) was very similar to the gut microbiota of healthy 30 year olds.

Lifestyle affects lifespan via epigenome; such epigenetic memory cannot be silenced with cognitive rationalization or neglect; by example, caloric restriction does change unhealthy DNA methylation patterns into healthy ones.

## 7. Results/Conclusions

Health must be understood for what it is - a personal responsibility, as well as what it is not - it is not health care; you can only buy health care but not health; yes, health care may keep you alive a little longer but it cannot make you healthy. Health is a harmonic rhythm of a biologic system that reflect organized complexity, generate value as its emergence from proactive optimizing relationships; health has to be earned. Key elements of a healthy biologic system are: 1-functional/semipermeable

boundary with active decluttering and, 2-healthy mitochondria, the energy powerhouse. Healthy lifestyle, with expectation of longevity, is an inseparable aggregate of diet, exercise, and stress management.

Longevity is the cognition-derived entrainment of individual's lifestyle with the principles of biologic systems. Health and longevity can only come through 'effort'; in spite of high expectations, longevity cannot be anticipated to come from drugs.

Contrary to a traditional belief, a genome has only a limited influence on longevity; the epigenome, the functional overlay over the genome, is what reflects lifestyle choices; most diseases are downstream manifestations of upstream etiology, consequences of decisions-influenced modifications of epigenome.

The 'road less traveled' to health and longevity, is through optimizing relationships that biologic systems have with their internal and external milieu, with self and others; if the former is not optimized/healthy, neither will be the latter; such connections are always evolving as we have to 'reassess and readjust', adapt and evolve, with what we initially inherited in 'genes and culture', and subsequently put a personal stamp on, spanning cognitive and epigenomic memory, all recorded as lifestyle choices that set the momentum that can carry health into longevity.

Integrity of biologic systems can be maintained in a dynamic, non-linear environment of life; several systems science doctrines, in an aggregate, point to a path of health and longevity. The major categories are: boundaries - hierarchies - upstream-downstream and decisions-consequences learning loops.

Semipermeable boundaries are essential for health and innovation; each morbidity, initiated by dysfunctional boundary, shortens life expectancy. Search for health must begin 'upstream' with realignment of existing cognitive 'framework for life' with systems science principles. Teaching 'how to make healthy decisions' is vastly superior to any attempt to 'control human behavior' or expecting medication to correct pathology that decisions initiated; such education must start with the understanding how to differentiate data into patterned information and finalize it with tailored intelligence to extract meaning. Most societies are increasing their population's education but not necessarily the level of their intelligence that include rationality and responsibility. Decisions-consequences connection is the most essential evolutionary learning loop, offering the ability to correct errors 'near-real time'.

Through the prism of systems science, Bell's theorem (1964) of inequalities, the difference of 'local realism vs. quantum entanglement', emerges and indicates that 'local realism' is a systems science downstream perception and the 'quantum entanglement' is the upstream, larger reality; the concept of quantum physics of entanglement resonates with systems science loop of 'decisions-consequences', as decisions are simultaneously 'setting up' the consequences, and are thus entangled, with both having the same 'spin' - healthy decisions have healthy consequences and vice versa.

It is all about choices - what and when to eat, what and how much to allow senses to capture and process, when and how long to sleep - these choices modify the function and structure of a biologic system as well as its 'personal world', the system's perceptual reality.



Many patients may encounter similar/identical diseases but those diseases often reach very different patients; some are healthy, those that keep tight connections between decisions and consequence as a learning loop, and those that do not and likely 'privatize' their decisions and 'socialize' consequences to the detriment to their health and longevity.

Global population's health continues to decline with demonstration of dysfunctional immune boundary, a consequence of chronic inflammation induced by obesity and other lifestyle choices; the pandemic of 2020 reflects these statistics; a health status mirrors the level of optimizing decisions.

'Chronologic time' is not the same as 'biologic time'. 'Age-related diseases' and 'time lived' are not causatively related; it is simply an association of two independent variables: 'chronologic time', the number of Earth's revolutions from birth to death, is independent of human decisions; 'biologic time' is 'lifestyle-related'; it reflects the impact of decisions and the accumulation of co-morbidities; 'age-related diseases' are primarily 'lifestyle-related'.

The gut microbiome matches the overall state of health; healthy microbiome is in synch with biologic time, unhealthy one simply follows the chronologic time; person's healthy gut microbiome reflects a young biologic age; a dominant number of cytotoxic CD4 T-cells in blood provides evidence of a life-long health.

Biologic cycles have optimal starting and ending points, refined by evolution, such as circadian day-night oscillations, metabolic phases, neuro-net's growth-regress of synapses, etc.; interference with these oscillations is detrimental to health.

Before any new cognitive memory can be 'constructed', some of the old ones must be 'destroyed'; cognitive memories are tied to synaptic connections in the neuro-net that must undergo weakening during healthy sleep, allowing new memory to be created the next day with strengthening of synapses; similarly, the epigenome must be prepared for new epigenetic markers stemming from lifestyle choice, in order to create its memory; here, the vitamin A and C participate in the demethylation of the epigenome, getting it ready to receive new memory-forming methylation marks. Asynchrony of cycles is detrimental to health: sleep asynchrony with day-night cycle, profoundly impairs old memories and the acquisition of new ones; similarly, night-time activation of metabolic cycle disrupts circadian rhythm in all cells.

All relationships are hierarchical and need to have a level-defined scope of influence; in a healthy societal system, vertical governing hierarchy only facilitates, while horizontal working hierarchy 'self-organizes'; if, however, vertical hierarchy controls/micro-manages horizontal hierarchy, it diminishes its potential for value creation with likely ultimate system termination. Similarly, individual cognitive decisions, the governing hierarchy of biologic systems, must refrain from attempting to control its periphery, its cells, as that stifles innovation, the life-essential state of adaptation and evolution.

Interval training opens the path to health and longevity as well as the development of specific cognitive, metabolic and muscle memories that lead to cardiovascular-cognitive fitness; it has three parts: intensive physical activity with caloric and information intake restrictions; it raises the physiologic threshold for

endurance, metabolic balance, and sensory input comprehension, all leading to extended physical, cognitive, sympathetic-parasympathetic systems balance with stem cells aptness, necessary for health, while enabling longevity. Aerobic exercise forestalls tissue hypoxia, which is detrimental not only to tissue survival but, it can also convert any, already present but differentiated, cancer cells into highly malignant undifferentiated cancer stem cell.

Perceptual reality is 'our own individual world', the way we see and relate to ourselves and the world at large; it is a cognitive emergence/outcome that decide what we 'see' in a given change and what we do about it. A decision is never made in isolation; it is based on the pre-set epigenome and the existing perceptual reality. Healthy perceptual reality is essential for meaningful conversion of majority of uncertainty into probability risk that generate a degree of rational optimism leading to optimizing decisions.

Health requires an upstream, systems science-based root-cause analysis, in order to prospectively judge, and be responsible for, the impact of decisions on the induced consequences.

Cycles of genealogy impact not only currently living adults but also have a transgenerational influence; via reproduction, epigenomic memory patterns for health or ill-health, are shared with the next generations; optimizing lifestyle choices by parents will make all the difference for them.

Evolution has continued to progress from 'hormones' to 'thinking' but this cannot be a one-way movement; these living cycles eventually regress - a reversal of 'thinking' as well as 'hormones'.

Healthy relationship with self has several components: 1-existence of decision-consequence learning loop, the upstream-downstream reciprocal connection, 2-absence of self-abuse, and 3- rationality and responsibility toward other systems of life.

Physical activity, tailored as '*enhancing*' interval training, is the only way that new muscle cells and brain cells, in the memory-critical hippocampus, can grow during adulthood; caloric and information restrictions, the '*subtracting*' type of interval training, allow these new cells full differentiation.

Healthy longevity requires biologic systems to maintain eloquent boundaries, principally controlled by cognitive decisions. There is no greater proof, of what sustained state of health can accomplish over time, than to extract the essence from those who had already lived '*century-plus10*' years. By comparison with general population, supercentenarians have been found to have four times as many cytotoxic T-cells, indicating a 'super-healthy' internal immune boundary, and a microbiome that resemble those in the 30s.

Let's make sure that whatever tradition has led us to believe is true, actually is; medicine cannot solve how and why people make unhealthy decisions but education can offer a foundation.

## 8. Results - Public Health Summary

Not much can be done about the date on a birth certificate but much can be done about the one on a death certificate.

If you don't spend time and money on your health, you will surely spend it on your disease; this truism is applicable not only to an individual but to a society as well, where the 'prevalence' matters.

There are over two billion people in the world who are currently obese; and, obesity is more detrimental to health than smoking.

Eat healthy during the day, 'when the birds sing and sleep when they sleep' (there is no learning without sleep); exercise 'as often as you eat' a healthy meal as both are needed for fitness. The word 'exercise' is too nebulous a word, escaping clear classification; for example, if you can talk on the cell phone and don't sweat, even if you're moving/exercising, you're not contributing to your fitness.

Excessive sensory input silences the mind through confusion.

Not everyone needs to be taught calculus but everyone should be taught how to make decisions, how to handle uncertainty; education would benefit from a reorient - from teaching 'downstream details' to 'upstream principles', as the 'details' will come out correctly when the 'principles' are set with the correct momentum for implementation. Inability to diminish/handle uncertainty leads to anxiety/paranoia with unpredictable outcome, including individual health, pandemics, riots, etc.; stress is an outcome of unmanaged uncertainty.

Beware of transgenerational influence of decisions. The work is cut out for you the day you are born receiving epigenomic modifications from your parents and ancestors; as soon as you are able to think, however, make decisions which are optimizing, pro-health; the power, over your behavioral choices affecting your health, will increase for decades but after about the age of 50, if you are still alive, the momentum is mostly set for the remaining state of your health and longevity.

Brain has access to only limited amount of energy, generated by mitochondria in cells, for signal processing regardless of the amount of food consumed; the brain has to decide how to spend it; for example, cognitive focus has higher metabolic needs, which can only come from simultaneously diminishing available energy to other non-essential brain regions; it is imperative to select what is indeed a priority, e.g. health, safety that protect and/or optimize your biologic system, and minimize any 'noise' that will clutter processing and drain energy.

Look at any food and ask: what's its connection to Nature's ongoing adaptation and evolution, a proven standard to measure sustainable life? For example, the principle of 'movement and intensity' is an essential for overall 'function and structure' of life; it can be translated as a food choice between fast moving fish or slow-moving cow, or which food contains genetic memory assuring evolution of 'structure' - here the option would be between seeds, tree nuts, whole grains, fruit vs. processed food; the farther you go from this comparative scale, the smaller its contribution to health.

You cannot look at your watch and tell 'what time it is for your body'; your biologic system runs on 'biologic time', which counts morbidities, and not on the 'chronologic time' of your watch.

## Notes

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