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How to reduce the dilemma between graceful aging and reverse aging

Thermo dynamical and biological background

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The purpose of writing is to point out the important aging topic and call the attention of federal NIH/NIA funding agencies and attention of younger scientists about the need of a treating aging as a disorder and toward reverse aging as recovery; otherwise, so many resources, in educations, in healthcare, in individual family life, will be wasted for a premature aging. On the one hand, this R/D will be important for 71.6 million aging WWII Baby boomer getting old circa 70 ~80 years in the US alone Figure 1a. Furthermore we mentioned an inevitable thermodynamic viewpoint about the entropy keeping increase until death, and the recovery information has been done, so far successful for single cell Yeasts[1] & Figure 1b. This aging might be biologically caused by losing digital or analog information.[2] There seems no specific procedure or medicine existed for slow down Homo sapiens aging toward revere aging. That's a reason we call the review as the dilemma to call attention to the concentrated studies in the next decades.

The Cloning should be done in next to Homo sapiens and is already too late to cloning for smart scientists: e.g. Landau and Lifshitz, and Einstein, etc. Sir Ian Wilmut have clones the Dolly the sheep Figure 1c with (three mothers: one provided the egg, another the DNA, and a third carried the cloned embryo to term) on 5th July 1996. Dolly's white face was one of the first signs that she was a clone because if she was genetically related to her surrogate mother, she would have had a black face.

Figure 1a 71.6 million WWII Baby Boomer; (b) Single Yeast[1] of the species Saccharomyces cerevisiae (In 1857, Louis Pasteur showed that by bubbling oxygen into the yeast broth, cell growth could be increased, but fermentation was inhibited – an observation later called the "Pasteur effect".) Several yeasts have been widely used in genetics and cell biology, largely because they are simple eukaryotic cells, serving as a model for all eukaryotes, including humans, for the study of fundamental cellular processes such as the cell cycle, DNA replication, recombination, cell division, and metabolism. On 24 April 1996, S. Cerevisiae was announced to be the first eukaryote to have its genome, consisting of 12 million base pairs, fully sequenced as part of the Genome Project. (c) Why clone the Dalley the sheep did not able to change the aging entropy of the mother sheep? Dolly was part of a series of experiments at The Roslin Institute that were trying to develop a better method for producing genetically modified livestock. Scientists at Roslin led by Professor Sir Ian Wilmut wanted to learn more about how cells change during development and whether a specialized cell, such as a skin or brain cell, could be used to make a whole new animal. Dolly was cloned from a cell taken from the mammary gland (so named after Dolly Patten) of a six-year-old Finn Dorset sheep and an egg cell taken from a Scottish Blackface sheep.

We mentioned the dilemma between life and death: namely between "fuzzy life" and "crispy death." Aging could begin at the birth or after the puberty. (a) birth to life and (b) getting old comes with the losing the information increasing the entropy, **(c)** aging to death. Henri Poincare pointed out the 2nd order in time-reversal invariant and Ludwig Boltzmann insisted the uniformity disinformation called the entropy always increases. While the 2nd order in time governing Newtonian dynamics are always reversible ($(\pm 1)^2 = +1$, but Nobel Laureates T.D. Lee and C.N. Yang pointed out both are correct, except at the initial and boundary conditions of every irreversible changes**.**

Mathematics model

Thermodynamics has been successfully adopted by John Hopfield independently Jacques Ninio but he resolved the dilemma by the biologically kinetic proofreading used in the genetics demonstrated otherwise the minutia amount energy difference between

$\exp(-\beta E_{C-G}) \approx \exp(-\beta E_{A-T})$ involved in the sharp digital A-T, C-G pairing information**.** That consume ATP to enhance specificity of various biochemical reactions for small binding energy error difference: A-T; C-G pairs) minimizing the entropy. On the other hand, the analogy information how 3 meter long DNA shall be wrapped in either explicit or implicit traits via Histone spooling and Methylation labels.

We believe the initial and boundary condition must be improved

by living habits: in 3 Physical dimensions: exercise daily, eat right, sleep tight: and 3 spirits dimensions: social often, stimulate brains, relax minds. All must be done efficiently in the sense minimizing the energy expenditure ΔE versus the entropy reduction ΔS according to the following theorem. Given the Boltzmann entropy $S = k_B LogW$, engraved on his headstone Figure 1a. An archeologist prefers the mountain-top rocks for the non-uniform information, than the uniform beach sands which has less information. In other words, Shannon information, as if the mountain top rocks, requires minimum entropy.

Theorem of graceful aging: Following D. Sinclair, the health trend requires both the digital genome DNA information and the analog epigenetic (Histone spooling and Methylatio) information. According Hopfield and Ninio the free energy probability model that is operated at the homeostasis temperature $T_0 = cons\tan t$ it must be associated with the minimum Helmholtz energy $\Delta H \cong 0$ so that we use the efficiently per usage of the energy expenditure ΔE to the decreases of non-information Entropy ΔS : The total probability of graceful aging is defined as

$$W = \exp\left(ST_o / k_B T_o\right) = \exp\left(\frac{E}{k_B T_o}\right)\exp\frac{\left(-\left(E - ST_o\right)\right)}{k_B T_o}$$

$$W = \frac{\exp\left(-\Delta H / k_B T_o\right)}{\exp\left(-\frac{E}{k_B T_o}\right)}; where\, \Delta H \equiv \Delta E - T_o \Delta S \approx 0$$

The efficiency η is estimated at the homeostasis temperature $T_0 = cons\tan t\, 37°C\ \ 300°K = \frac{1}{40} eV$

$$\eta \equiv \frac{\Delta S \downarrow}{\Delta E \downarrow} \cong a T_0^{-1}$$

where the proportional constant is the degree of efficiency

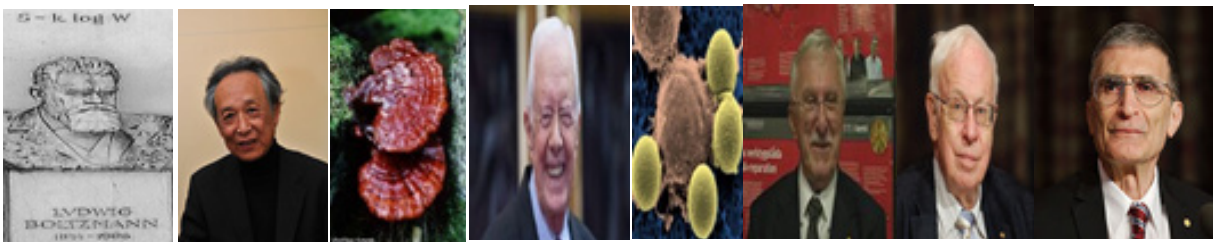
$$a \approx 1 \square 10$$

We conclude the gracefully aging must be efficient in the energy effort $\Delta E \downarrow$ to reduce the aging dis-information $\Delta S \downarrow$ Q.E.D.

Antiquity Goal of Reverse Aging: On the one hand, we believe the graceful aging, on the other hand, we are aware of the holistic Herbal medicine with Westin compartmental treatment medicine. While both are worked on human immune systems, the key difference is mainly in the time duration that the holistic nature which is slow in herbal drug for years versus fast western target drug in months. There is an old saying:"when you are sick, seeking Westin medicine; when you are not, the herbal medicine." Hopefully there are some rejuvenated medicines reverse aging for initial boundary conditions. For example, the global villagers have practiced the FDA(www.fda.gov/medwatch) -approval birth control hormonal (e.g. Annovera with 97% effective) over decades with less born. Moreover, the so-called "reverse aging" effect in the human protocol: "Targeting Aging with Metformin" (TAME) clinical trial since 2017 led by Albert Einstein College of Medicine's Dr. Nir Barzilai and colleagues from Wake Forest School of Medicine. (cf. BBC World News interviews Dr. Nir Barzilai using original Diabetics II (body having the insulin but timing may be missing drug) called "Metformin", made of water-soluble lilac).

Moreover, the DNA replication, immune system specificity, enzyme-substrate recognition among many other processes that require enhanced specificity. The DNA repair ability of a cell is vital to the integrity of its genome and thus to the normal functionality of that organism. Many genes that were initially shown to influence life span have turned out to be involved in DNA damage repair and protection. The 2015 Nobel Prize in Chemistry was awarded to Tomas Lindahl, Paul Modrich, and Aziz Sancar for their work on the molecular mechanisms of DNA repair processes.[3-6]

Figure 2a Ludwig Boltzmann Head Stone define the Entropy



S; the Herbal Mushroom G Lucidum, Lingzhi (that 2000 Nobel Laureate Literature Mr. Gao Xingjian recovered in cancer) similar to Merck immunotherapy Keytruda (Pembrolizumab) drug (that President Jimmy Carter Liver and Brain Metastasis cancer: Aug. 2015 ~Feb. 2016)? While Merck drug (Yellow balls) are targeted at the Programmed cell Death 1 (PD-1) receptor and allows body's own immune system go after the cancer cells; (b) 2000 Nobel Laureate Literature Mr. Gao Xingjian recovered in cancer1 (c) Herbal Mushroom G Lucidum, Lingzhi. similar to (d) President Jimmy Carter Liver and Brain Metastasis cancer: Aug. 2015 ~Feb. 2016 Merck immunotherapy Keytruda (Pembrolizumab) drug (e While Merck drug (Yellow balls) are targeted at the Programmed cell Death 1 (PD-1) receptor and allows the body's own immune system go after the cancer cells (f) 2015 Nobel Prize of Chemistry for DNA Repair to Paul Modrich, (g) Tomas Lindahl and (h) Aziz Sancar.

As yet, not a definite experimental proof exited, beside single cell yeasts, for aging and reverse aging, we call the issue at the Homo sapiens level as the dilemma. We begin with a simple telomere, a structure at the end of chromosomes that protects the chromosome that according to Nobel Laureates Elizabeth Blackburn, the peaceful emotional response might keep us the telomerase for graceful aging. Thus, to support this emotional aspect, we recommend 5G communication embodiment to keep us connected and happy with loved one. This 5G can be empowered beyond *video imaging* via *current mini-meter carrier wave* communication to keep us connected virtually and emotionally happy.

Future experimental efforts

(1) Since we know that Telomeres are 'caps' on the ends of Homo Sapiens DNA molecules, called 46 Chromosomes in 23 pairs (XX female for XY for male) that protect the DNA from damage, Dolly telomeres were shorter than Leonard Hayflick in 1961 50 turns

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expected for a normal cells. (Pluri-potent stem cells are embryonic stem cells capable of differentiating into any embryonic cell line of any of the three cell layers). Hayflick was the first to report that only cancer cells are immortal. This could not have been demonstrated until he had demonstrated that normal cells are mortal. Cellular senescence does not occur in most cancer cells due to expression of telomerase enzyme. This enzyme extends telomeres, preventing the telomeres of cancer cells from shortening and giving them infinite explicative potential. In fact, a proposed treatment for cancer is the usage of telomerase inhibitors that would prevent the restoration of the telomere, allowing the cell to die like other body cells. As an animal or person ages, their telomeres become progressively shorter, ***a*** *sign of aging*, exposing the DNA to more damage. Three key factors of aging: (a) aforementioned shorter *Telomere***s**, (b) Mitochondria damaged by Reactive Oxygen Species, (c) Genomic instability damage goes unnoticed and gets passed onto new cells created an imbalance. (Surface signs of wrinkle of skins are not known to reflect aging but it did blame keratinocytes & collage). In 2004, Charles Brenner discovered a vitamin B3 (Nicotinamide riboside, a micronutrient) that increases NAD+ (Nicotinamide Adenine Dinucleotide) to continue promoting telomere function and genome stability, which extended lifespan in ***yeast***, and should have protocol to be applied to aging baby boomers.

(2) Slowdown aging seems to be possible by means of accurate recovery of digital codec information proposed by James Watson and Francis Crick as well as Rosalind Franklin in 1953, Cambridge Univ. using X-ray determined the double-helix structure of DNA genome (A-T, C-G, DNA, e.g. accurate recovery of 40 thousand years old Neanderthal info). On the other hand,[1] the phoneme, namely epigenome has been postulated early by Conrad Waddington Cambridge in 1942 how the 6 foot long genome is wrapped along tiny protein balls called Histones spooling, tagged with Mythelation CH_3) as analog heredity traits. Nonetheless, the degradation of both digital and analog information *cause the aging*, cf. David Sinclair, et al.[2]

(3) A resolution of the dilemma between (a) Life and birth & (b) Aging and death, we may have to consider repair as if were the re-set the initial condition reproducing life's (from the part of nature that are governed by the universe mathematics). Nonetheless, the life can be modified within the narrow initial and boundary conditions of the irreversible thermodynamics through proofreading and DNA repair chemistry, but the analogy information that still need a way to do better than TAME.

(4) Since aging is not a disease, herbal medicine over thousands years should be adopted for better maintenance and reacquisition of quiescence are defining features of Homo sapiens adult stem cells, beyond the success at the yeast level. In fact, Prof. Andrew Black of UCSF[7-9] are studying the intrinsic muscular rebirth during muscle homeostasis, injury response and aging and extrinsic 10 degree of freedom that control quiescence and how they impinge on self-renewal and differentiation potential.

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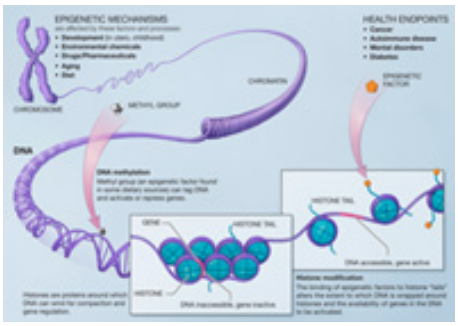
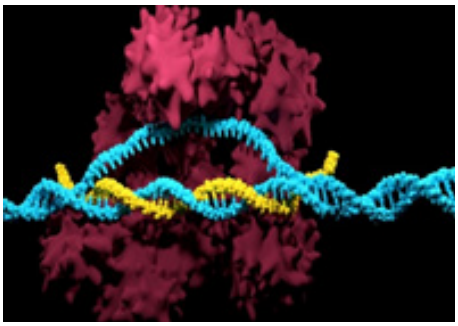
Appendix

The dilemma exists between gracefully aging and reverse aging, between the digital genome information of DNA (A-T, G-C pairing wined to mm size and untwined in 3 meters long), and analog phenome epigenetic (outside) information including losing the DNA Methylation tags for graceful aging, and Chromatin/Histone spooling modifications for aging: cf. Fig. A: Chromosome carried the digital Genome to analog epigenetic phenome, ala David Sinclair: " Lifespan: Why We Age, Why We Don't Have To" (National Best Seller 2020); Fig. B: Nobel Prize in Chemistry 2020 was awarded to Emmanuelle Charpentier (left) and Jennifer A. Doudna(right); Fig. C: schematic drawing of Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)"/Cas9 (an enzyme that cut double strand DNA and Protein).





Nobel Prize in Chemistry 2020 was awarded jointly to Emmanuelle Carpenter (left) and Jennifer A. Doudna (right who studied at Harvard for her Ph D, under Laureate Jack W. Szostak (whose crystallization for X-ray imaging technique has supported Elizabeth Blackburn, & Carol W. Greider to receive 2002 Nobel Prize for their work discovery of Telomerase Enzyme to replenish Telomere to keep Chromosome neatly tight up in the so-called Hayflick turns). Likewise, it's all in the family, Dr. Doudna applied the X-ray crystallization methods to the discovery how to perform genome editing.

There is obvious a dilemma occurred, namely the classical Darwin fittest-survival evolution will be taken over by man-made "artificial evolution." This kind of gene therapy revealed how the virus attacked the bacterial; like-wisely Severe Acute Respiratory Syndrome (SARS) CoV2 virus with spike protein (known as Alpha, Beta & Delta CovID-19) attacked human, by injecting their m-RNA into targets, either bacteria or human, to reproduce themselves. This phenomenon likes a two-edge sword, which can be beneficial in medical gene therapy for disease treatment, and also it touched upon the ethic issue of "playing god" –e.g. to reproduce heartless brave soldiers.

This playing god Dilemma might be traced back to Molecular Theory of Darwin Evolution by Gene Therapy or Gene Editing techniques called "Clustered Regularly Interspaced Short Palindromic

Repeats (CRISPR)"/Cas9 (an enzyme that cut double strand DNA and Protein)

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