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Research Article

Towards Quantum Medicine

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Abstract

In this paper we review the progress made in the area of quantum biology over the past two decades. We then outline the possible consequences of quantum biology on the understanding of human physiology and potential for major advances in the practice of medicine, especially in relation to chronic diseases such as diabetes, cancer and neurodegenerative diseases.

Introduction

Western medicine and pharmacology have achieved amazing successes diagnostically and therapeutically by applying strategies based on a direct cause-and-effect relationship, which work especially well in acute care settings. Algorithms for treating seizures, cardiac arrest and respiratory failure, the development of antibiotics and analgesics are examples of very successful applications of these strategies in medicine. However, particularly in the area of chronic diseases such as cancer, neurodegenerative diseases and diabetes further strives now require new perspectives predicated on insights from molecular biology, systems biology and even quantum physics. Recently, major progress has been made in our understanding of biological systems due to the atomistic representations of proteins, DNA RNA and other biomolecules. Physics has achieved extraordinary explanatory insights into the nature of physical reality, and now quantum concepts are steadily making their way toward elucidation of how biology works in terms of its interacting components. This promises game-changing developments in the life sciences that will profoundly affect medicine and pharmaceutical sciences in the future. Quantum mechanics as the most fundamental theory of matter provides non-intuitive and quantitative predictive tools for our understanding of both inanimate and animate systems. The term quantum was introduced to represent energy quantization of microscopic objects. Quantum entanglement defines a situation where two or more wave functions of microscopic particles form a composite state such that acting on one of them instantaneously affects the other. A quantum system is viewed as a combination of multiple states corresponding to different possible outcomes when we try to measure its properties. However, quantum mechanics is not limited to microscopic objects but can also apply to properties of matter at macroscopic dimensions and at physiological temperatures. Quantum physics provided a clear description of the periodic table of the elements and gave rise to quantum chemistry by explaining atomic valence states and the formation of chemical bonds between atoms. Chemistry is based on the creation and destruction of bonds between atoms in molecules and hence it relies on quantum interactions. Since biochemistry is an application of chemical principles to organic molecules, this brings us close to biology and provides a plausibility argument for quantum biology. Moreover, quantum physics transitions smoothly to classical physics when differences between energy levels become infinitesimally small, but it is not clear where a boundary between quantum and classical worlds exists. A growing number of macroscopic phenomena such as superconductivity, superfluidity, laser action and permanent magnetism have been demonstrated to be quantum in nature. Quantum tunneling refers to the ability to cross over and penetrate a potential barrier in situations when microscopic particles do not have enough energy to do so according to classical physics. Indeed, it is their quantum wave function that exceeds the confines of the potential in which the particle is trapped. An application of this property to cell biology, for example to the problem of potassium tunneling across ion channels in the cell membrane has already been contemplated. Since there are thousands of ion channels in a cell separated by only small distances separating them, coherent ion channel tunneling could explain the synchronization of ion waves across and between cells. With no size limitation to quantum effects in principle, biological systems are viable candidates for the application of quantum concepts, both literally and metaphorically.

Although quantum theory is based on probabilistic principles, even when applied to a single particle, there is also a statistical aspect for systems of many quantum particles. In the case of a single particle, we never know for sure what the exact state of a particle is. What we only know are the probability values for its states and their time evolution. In the case of many particles, we can compute macroscopic averages over an ensemble of these particles. This is similar to the difference between individual variability for the state of health of a patient and statistical variability for a population of patients determined by epidemiology studies. It is the scale of macroscopic averages where we find the greatest potential for employing quantum effects in biology. The assumption that a macroscopic-scale quantum mechanics can be applied to biological systems forms the basis for the emerging field of quantum biology. Its implications promise to be ground-breaking for understanding health and disease.

Biology deals with living systems, which are comprised of water molecules and biomolecules, functioning at the mesoscopic and mac

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roscopic scales and at relatively high temperatures. However, neither the sizes of living systems, nor their complexity, nor the degree of fluidity, nor even the constant presence of thermal fluctuations prevents the applicability of quantum mechanics. Quantum physics notions of discreteness, tunneling, superposition and entanglement allow for novel perspectives within the biological applications.

The Emergence of the Quantum Biology Paradigm

Biology today is at a point in its development, which is analogous to physics a century ago. It has accumulated a massive amount of data but has not yet provided a framework of organizing principles for quantitative understanding of the data. Today molecular biology, genetics, cell biology, etc. collect reams of real-life data that only computational methods can organize. Schrödinger in his seminal book "What is Life" [1], stated that classical physics appears insufficient to explain the organizational and functional efficiency of biology. He proposed that life's unitary oneness may stem from quantum coherence involving biomolecular components. Hence, life represents "order arising from order" rather than "order emerging from chaos".

Quantum mechanics explains the structures of chemical molecules and the strengths of their chemical bonds as well as details of the mechanisms of chemical reactions. However, no fundamental life principle has yet emerged from the quantum investigation of biological systems that can single out the living state in any special way. Furthermore, classical molecular mechanics models of proteins, DNA and other biomolecules aided by Newtonian mechanics descriptions of their constituents seem adequate for applications in molecular biology. However, quantum physics is expected to provide biology with conceptual tools that can explain the emergence of such properties as coherence, tunneling and entanglement. Superpositions of quantum states may elucidate the reason for rapid rates of protein folding processes and reasons for hot spot gene mutations. Entangled states can be found in brain dynamics and human cognitive processes. Tunneling play a role when electrons efficiently find their way to reactions centers in photosynthetic complexes or in mitochondrial wall proteins. Moreover, quantum processes may also exist on larger scales which, could explain biological and physiological synchronization and coordination of activities across an organism. However, biological systems' complexity makes it hard to separate quantum from classical effects which may coexist. For example, there could be both a classical and quantum component to a ligand-receptor interaction. The latter becomes important only over a short-range while the former is relevant to long-range interactions. Quantum interactions may facilitate processes that are too slow or even impossible within classical physics. The advantage of quantum coherence is to enhance spatio-temporal coordination of processes, which could provide an explanation of an organism's "unitary sense of self". Another important and largely unexplained issue of the faithful amplification of quantum coherent modes from a microscopic to a macroscopic level. For example, a single photon triggers an electronic excitation in the rods and cones of a retina [2], which then causes a reaction in the brain that is perceived as a flash of light. The question still remains regarding a specific mechanism of amplification of individual quantum events involving photon-receptor interaction, which leads to classical macroscopic effects at the level of the human brain. Moreover, evidence exists that olfaction is based on a quantum resonant energy transfer mechanism involving vibrational degrees of freedom of aromatic molecules and receptors in the membranes of olfactory nerves [3]. This mechanism is different from the traditionally accepted lock-and-key mechanism of receptor-ligand interactions [4], which does not rely on quantum physics.

Generation of organism-wide coherence can involve quantum mechanisms at several levels whereby multiple elements can be coordinated within a unit and then these structural units become synchronized in a hierarchical manner. This is due to a vast span of timescales over which biological systems operate: ps (10^{-12} s) oscillations of H-bonds, μs (10^{-6} s) changes of conformational states of proteins, ms (10^{-3} s) operation of action potentials, second-scale for the human senses, an hour-scale of cell division (10^{4} s), the life-span scale (10^{9} s). Hence, biology encompasses 21 orders of magnitude on the time scale. In parallel, spatial dimensions in biology range from atoms on the angstrom scale (10^{-10} m), to proteins on the nm scale (10^{-9} m) to cells on the μm-scale (10^{-6} m) to organisms on the meter-scale. Hence, spatial dimensions of living systems span 10 orders of magnitude.

However, environmental decoherence caused noisy thermal environment in biological systems must be overcome by some very sophisticated mechanisms. Quantum de-coherence represents loss of frequency and phase synchronization. Frequency is important because most biological processes are cyclical. Phase is important for coupling cyclical processes whereby being out of phase causes destructive interference. However, biological systems might be less susceptible to decoherence than physical systems under similar conditions because biological organisms are non-linear, open, driven systems that function under far-from equilibrium conditions. Coherence is possibly maintained by a sufficient rate of energy supply in the form of metabolic energy due to nutrients. Additionally, thermal noise shielding may diminish random noise, and this may involve structured water, which resembles two-dimensional ice more than a random three-dimensional fluid. More than 50% of water molecules in cells form quasi-two-dimensional structures whose dipoles form a hexagonal lattice with long-range dynamical order [5]. Such structured water [6] may be amenable to quantum mechanical properties in biological systems and may be conducive to transferring information between disparate regions of the body. Moreover, natural evolution over billions of years of endless experimentation via trial and error may have solved the problem of decoherence of quantum states using mechanisms that we are not yet aware of.

In general, the term quantum biology refers to the application of quantum mechanics to biological systems and processes based on nontrivial aspects such as: 1) superposition; 2) tunneling; 3) entanglement; and 4) non-locality. For example, Beck and Eccles developed a quantum model [7] of neurotransmitter release by neuronal synapses in the cerebral cortex. These authors represented tunneling of electrons as triggers for exocytosis between the presynaptic and the postsynaptic neuron. Some proteins contain active sites contain residues that are involved in hydrogen bonding interactions, and to reach the sites, the hydrogen atom has to navigate a complicated potential energy landscape, which can be enabled by quantum tunneling. Vattay et al., [8] proposed that life has evolved by exploiting protein behavior positioned at the thin edge of the edge between quantum and classical behavior, called quantum criticality. Also, mutations may drive evolution, using quantum processes that provide an evolutionary advantage by employing rapid search algorithms to obtain optimal solutions.
Nature is the master of nanotechnology, which has created proton pumps, nanoscale rotary F-ATPase enzymes, motor proteins and DNA polymerases, among other nanomachines. The examples of nanoscale quantum biological systems and processes that have been

closely examined include photosynthesis [9] with its complex light capture structures in the chlorophyll, motor proteins forming the machinery of a living cell, as well as effects of metabolic enzymes, ion channels, etc.

The biological analog of the photoelectric effect is photosynthesis. It involves the capture and transformation of light energy into biochemical energy. Photosynthesis is a sophisticated well-tuned mechanism that harvests light energy to split the water molecule and create a cascade of reactions. The process is very efficient due to its fine-tuned design of a physical system, which attained near-optimal performance. An important feature of photosynthesis is that the molecular architecture involved is structured to exploit long-range quantum effects over several nanoseconds, which is sufficient to deliver energy quanta to the reaction center. These reaction centers capture individual photons and transfer exciton energy by tunneling avoiding decoherence at ambient temperatures [10]. Light harvesting complexes exhibit a symmetrical geometrical arrangement of chromophores in chlorophyll pigments [11] operating at nearly 100% efficiency due to sharing excited electrons across the chlorophyll network. Bio-chromophores other than chlorophyll are pyrroles, porphyrins, cytochromes, carotenoids, ferredoxins, flavins, heme and melanin. Additionally, among naturally-occurring amino acids three possess fluorescent chromophoric properties: tryptophan, tyrosine, and phenylalanine, and contain resonance ring structures in which electrons are delocalized and can be used as sites for electronic energy transfer. Intra-molecular energy transfer processes involving tryptophan, tyrosine and phenylalanine residues occur in protein structures leading to efficiently transfer energy between chromophoric residues [12]. Similar processes may take place in proteins (tubulin and actin) and protein polymers of the cytoskeleton, i.e. microtubules and actin filaments [13]. Quantum mechanics provides a relative reduction of a time scale such that energetic expenditure involved in the inspection of the information space of probabilities occurs relatively fast compared to classical information searches. Hence, if biological phenomena were to fully exploit the possibilities contained in quantum physics, they could occur virtually instantaneously with extraordinary synchronously coordinated structure-function relationships. Quantum systems, especially those capable of quantum coherence, relative to thermodynamic systems lose very little energy to heat and hence entropy production making them very appealing as blueprints for biological function. An entire organism can be both mechanically and electrically linked in an interconnected electromechanical matrix that allows for long-range mechanical and electrical signal transduction. It is worth mentioning the important role played by the extracellular matrix, which defines the space between cells and forms connections to the cell's interior through integrins, which are membrane proteins connecting with the intracellular cytoskeleton via receptor-based signaling processes. The cytoskeleton, in turn, connects between the cytoplasm and the cell's nucleus forming a dense network of mechanical cables that may also act as electrical wires for ionic conduction [14].

The use of quantum processes occurring in plants and bacteria is expected to have been retained through evolution in higher-developed life forms including humans. Quantum biology recognizes the entanglement of parts forming the whole organism, hence entanglement may be the unifying principle that, due to coherent supply of energy to living systems, integrates the entire sum of the cells into a functioning organism.

Biophotons

Photons are emitted by all living and non-living systems in the form of black body radiation due to the heat absorbed and emitted by the molecular and atomic oscillations taking place in these systems. The concept of biophotons was introduced by Alexander Gurvitsch and defined as specific electromagnetic waves emitted by living systems as a result of their metabolism and other functions such as cell division, which are exclusive to animate matter. Biophoton intensity is proportional to the amount of radiation in excess of the black-body emission at a given temperature. Subsequently, Popp [15] demonstrated that photons can be both absorbed and emitted by DNA in the form low-intensity ultraviolet radiation. Albrecht-Buehler [16] showed that living cells can detect near-infrared electromagnetic waves at around the wavelength of 1000 nm, and proposed that mitochondria release these photons as by-products of metabolic activity. Biophotons could be viewed as a quantum form of bio-electromagnetism, which could be responsible for long-range coherent effects of mitochondrial electron transport chain ATP production. The sources of biophotons could also involve free radical recombination of reactive oxygen and nitrogen species or the relaxation of excited electronic states. Neurons are known to continuously produce photons during their metabolism, and the intensity of photon emission from rat brain correlates with cerebral energy metabolism, electrical activity, blood flow, and oxidative stress. Importantly, weak bioluminescent photons can propagate along neural fibers [17] suggesting their potential involvement in neural communication. Biophotons can be used to enhance adaptive protective effects in living cells. Mitochondrial electron transport chain contains several chromophores, especially the porphyrin rings of cytochrome oxidase (complex 4). The absorption of biophotons by these photosensitive molecules can produce an electronically excited state, which has very different chemical and physical properties compared to their electronic ground state. In this case, the absorption of biophotons within mitochondria occurs in close proximity of the origin of photon emission. The electromagnetic field emission is an associated aspect of cell metabolism. This involves the proton pump in the cytochrome enzyme whereby a passage of a proton from a higher energy state to a low energy state causes a photon emission in the near infrared range, which is a distinct mechanism of biophoton generation from that involving recombination of reactive oxygen species. Molecules containing iron are contained in complexes 1, 2 and 3 of the mitochondrial wall while both iron and copper are contained in complex 4, which is cytochrome oxidase. It is intriguing that these roughly 1000 nm wavelength biophotons have an energy level equivalent to about two ATP molecules. Consequently, they may be important in facilitating enzymatic catalytic activities in the cell. Biophotons may be responsible for spatio-temporal correlation of quantum metabolism. That is, they may provide the energy for motor proteins to move mitochondria along microtubules in a spatially correlated manner. Biophotons may also catalyze the movement of other electrons from their NADH or $FADH_2$ donors of other electron transport chains within the same cell across mitochondria and even between cells in a temporally-correlated manner. This insight supports the idea that electromagnetic fields projected by the electron transport chains may have a role in synchronizing metabolic activity between mitochondria and even between cells and tissues. While an electron transport chain emitted magnetic field is likely to be weaker than a biophoton, it is again unlikely that nature would not have intended to have a purpose for it. In fact, a multipurpose maximally-efficient organizational value of such mechanisms is likely to have been retained over two billion

years of evolution. Due to very low intensities of the biophoton emission compared to the flood of photons bathing the environment, these effects are extremely hard to detect.

Biophotons, not unlike ATP, could provide an ample supply of energy that can be utilized by cellular process. While biophotons can provide a similar amount of energy to that which ATP provides, they are less localized in space and hence play a greater role in orchestrating synchronized coherent activity within and across cells. For example, this could assist in transporting electrons from reactions in the TCA cycle to NADH or $FADH_2$ to the electron transport chain in complex 1. However, in the context of metabolism and biology, such as the role of biophotons as promoting synchronous, coherent ATP production, nuclear transcription and other metabolic activities, much still needs to be explained. Perhaps if many biophotons are released simultaneously, electron transport chain oscillation frequency may be maintained in synchronous coherent fashion such that the collapse of the wave function with each particular biophoton effects only mitochondrial enzyme oscillations that otherwise would not keep pace.

There may be distinct electromagnetic mechanisms operating inside the electron transport chain. First, biophotons may be generated from the recombination of reactive oxygen species or alternatively from the heme excited state of electrons making their transition back to the valence orbital from the conduction orbital. Consequently, biophotons and electromagnetic effects in cells may be involved in a mechanism that synchronizes larger scale bioenergetics involving numerous mitochondria within a cell, cells within tissues and eventually different organs and tissues within the body.

Quantum Metabolism

Energy transduction in plants involves light harvesting through chlorophyll while animals predominantly utilize glucose metabolism in mitochondria and glycolysis in the cytoplasm. Interestingly, the structure of chromophore molecules, which trap light energy within the chlorophyll in plants is similar to those present in mitochondria but instead of excitons, electron transport chain mechanisms of energy production is used to generate ATP from ADP. It is, therefore, suggestive that mitochondrial oxidative phosphorylation may involve quantum energy transfer. It is worth noting that mitochondria exhibit great organizational complexity since they comprise five complexes embedded within the inner mitochondrial membrane where quantum electron tunneling takes place.

Living systems exist at far-from-thermodynamic-equilibrium conditions whereas nonliving systems rapidly achieve thermodynamic equilibrium. The former require sustained energy supply in the form of light (plants) or usable nutrient molecules (animals) in order to be able to transduce this energy supply into chemical, structural, osmotic, electrical and mechanical work, which is essential for survival. However, body size introduces major constraints on the rate of energy transduction. Allometric laws of physiology describe mathematically how metabolism scales with the size of a living system, both within and across various species. Metabolism in unicellular organisms, plants and animals has a scaling exponent, which is somewhat dependent on taxa and it ranges between 2/3 and 1 with ¾ being the most common value. A quantum mechanical explanation of allometric scaling laws was developed [18] based on the cyclical nature of biochemical reactions within the metabolic chain. Production of the metabolic energy quantum, i.e. ATP (equivalent to approximately 10^{-20} J) involves synchronized coupling of two molecular reaction chains: (a) the redox chain where transfer of electrons between redox centers within the electron-transport chain occurs, and (b) the ATPase motor activity, which phosphorylates ADP to ATP. This process involves electron transport and is called oxidative phosphorylation. An alternative, much less efficient process of energy production is purely chemical and is called substrate phosphorylation. These are cyclic processes whose characteristic transit time, τ, determines the metabolic flux, which is understood as the number of proton units released by these reactions. Oxidative phosphorylation is coupled to the pumping of protons across the mitochondrial membrane that generates an electrochemical gradient (pH difference). However, substrate phosphorylation takes place in the cytoplasm and is driven by enzymes that couple ADP phosphorylation to the electron transport chain. Hence, the energy generated by the redox reactions gives rise to synchronized oscillations of metabolic enzymes. Quantum metabolism is a mathematical formalism which provides a microscopic explanation of allometric scaling laws of physiology by invoking a mathematical analogy with Planck's quantization principle that gave rise to quantum physics. It states that the metabolic energy of an enzymatic oscillator with frequency ω is quantized according to the formula $E_n = n\kappa\omega$, where κ is a biological analogue of Planck's constant. Quantization of metabolic energy is directly related to the fact that only integer numbers of ATP molecules are produced by the cell.

Metabolic rate changes depending on the external and internal conditions the organism experiences. The maximum metabolic rate defines at a molecular level the characteristic cycle time, denoted t*, which is the shortest period of time over which metabolic enzymes restore their active conditions. This is equal to the maximum turnover rate for these enzymes and it establishes a rate-limiting process within cell metabolism. Two limiting behaviors have been found for metabolic scaling laws: (a) in the quantum limit the cycle, time t is much longer than the characteristic cycle time t*, whereby $P = \alpha W^{\beta}$ where is the characteristic exponent for the metabolic rate P in relation to weight W, and α is the proportionality constant [19]; (b) in the classical limit the cycle time t is much shorter than the characteristic cycle time t* that corresponds to the maximum rate of enzymatic turnover. In the classical limit, the metabolic network is over-supplied with nutrients, and the biological system reaches a saturation limit. This can be viewed as a pathological case when electron leakage occurs resulting in an increase of the reactive oxygen species and oxidative stress, inflammation, acidity, and impaired energy production. We can say that the classical limit is a signature of pathogenesis. Conversely, in the quantum limit, the system is energy under-supplied whereby the metabolic enzymes "run on empty", i.e. they cycle faster than the rate of nutrient delivery. However, most of the time the biological system operates in between these two limits ($\tau > t > t^*$). The quantum limit corresponds to the greater efficiency since the metabolic rate increases at a rate lower than the increase in the size of the system. The associated lower caloric demand is due to collective efficiency of organs and tissues considered to be well-integrated parts of a well-functioning organism. When this coordination of cellular activities is lost, this requires a high nutritional demand as is the case, for example, with malignant tumors. Another example involves a vigorous cardiac output from myocardial contraction in normal sinus rhythm, which is a coherent and correlated contraction of muscle fibers with an intact conduction system. This is consistent with the quantum regime. On the other hand, when the conduction system is arrhythmogenic, the muscle fibers no longer contract in synchrony. The resultant fibrillating desynchronized contraction represents a transition to the classical regime with a much less efficient function.

ATP is a universal biological energy unit used to produce work through hydrolysis via a quantum mechanism. A mole of ATP synthesis requires about 60 kJ of energy. The corresponding cycle time for energy transduction in biological cells ranges between 10^{-6} to 10^{-3} seconds. Hence, one mole of ATP is generated in 3 to 7 seconds. Coherence and synchronicity on a macroscopic scale of ATP energy production amounts to optimal efficiency of biological energetics. When metabolism relies on the glycolytic mode as opposed to oxidative phosphorylation, the oscillation frequency of metabolic enzymes is slower and the efficiency drops down. Glucose is used to produce ATP in a series of coupled reactions, either glycolysis or oxidative phosphorylation (OxPhos) providing energy, which becomes stored in ATP molecules. While most of this energy is transformed into useful work, some is dissipated to maintain physiological temperature or lost to heat that escapes into the environment. OxPhos produces a much higher ratio of useful energy compared to dissipated heat than glycolysis but the glycolysis is faster as measured per cycle of substrate conversion to product with glycolysis being many times less efficient as per the amount of ATP produced per molecule of glucose. The efficiency of nutrient fueling mitochondrial oxidation is gauged by the P:O ratio, i.e. the amount of ATP produced per oxygen consumed. This ratio is higher for glucose oxidation than for fatty acid oxidation. Although OxPhos is slower than glycolysis, it is due to its coherent synchronization across the organism. Hence, the greater efficiency of energy production in the quantum regime is seen as a function of a higher P:O ratio in addition to a greater amount of infrared energy released from the hydrolysis of ATP captured in biological work. Thus, less energy is lost as dissipated heat in the process of ATP production.

Quantum Decoherence and Disease

The above analysis reveals potential consequences from a clinical perspective in terms of overloading mitochondrial capacity and a feed-forward process of mitochondrial dysfunction and reliance on glycolysis for the needs of ATP production. As a result, overload of nutrient consumption cannot feed into the mitochondria and energy production is forced to rely on the glycolysis pathway. Therefore, above the "take-over" threshold, mitochondrial ATP production follows a classical metabolic regime, which is less efficient because it is less coordinated. Cytosolic substrate level phosphorylation is always less efficient than oxidative phosphorylation.

Free radicals constitute important sources of biophotons in the human body. They are byproducts of metabolism and their recombination leads to the emission of biophotons. Hence, since free radicals are produced predominantly in mitochondria could have both negative and positive effects on cellular health. At low to moderate levels, they could enhance quantum metabolism *via* production of biophotons through recombination. However, when overproduced due to over-nutrition, they can be associated with inflammation, which is a source of excess heat. This can then result in the collapse of a superposition wave function that degrades the synchronous coherent oxidative phosphorylation metabolism.

In terms of the allometric relationship between metabolic rate and weight in humans, as weight increases excessively, the β scaling exponent is reduced, which could signal a slower metabolism and thus contribute to the mitochondrial dysfunction associated with metabolically unhealthy obesity. The latter is characterized by insulin resistance metabolic syndrome and often type 2 diabetes whereby reduced metabolic rate parallels lower reliance on mitochondria. This ultimately results in a well-defined relationship between insulin resistance and diabetes with cancer and Alzheimer's Disease (AD). Both cancer and Alzheimer's Disease (AD) include a major metabolic aspect while being metabolic "opposites" of each other due to the different directions of the metabolic shifts involved. The Warburg effect takes place in the cancer setting and "anti-Warburg" effect is characteristic for AD [20]. The Warburg effect represents a shift in the energy production from oxidative phosphorylation to glycolysis. The anti-Warburg effect is a shift in the opposite direction, i.e. from glycolysis to oxidative phosphorylation. Cancer as a metabolic disease associated with the Warburg Effect, which underscores the importance of dietary restriction., Consequently, dietary restriction preserves mitochondrial function and favors the more efficient energy metabolism. The role of mitochondria is important not only in cancer, but also in AD. Metabolic disturbances such as insulin resistance and type 2 diabetes are associated with impaired mitochondrial structure and function. Hence, it makes sense to conclude that cancer and AD are associated with insulin resistance in type 2 diabetes (DMII). As discussed above, maximum metabolic efficiency is linked to quantum mechanics. All living systems stay alive by overcoming the second law of thermodynamics (increase of entropy), which is accomplished by energy expenditure to minimize damage and structural degradation. Conversely, a transition from a healthy state to a pathological one involves entropy increase. This can be shown quantitatively mathematically for malignant tumors at all levels of biological organization, i.e. from the proliferation of somatic DNA mutations to the increased complexity of protein signaling networks, to the disordered cell morphology and even tissue dis-organization. Additionally, entropy increase is also seen in the inefficient form of metabolic energy production causing heat dissipation. Finally, a progressive entropy increase, which eventually results in the state of death.

While quantum metabolism theory has been centered on the metabolic energy production, the other side of the equation involves energy consumption. Both energy production and consumption combine into a totality of metabolic processes. Therefore, we propose the existence of both classical and quantum modes of energy consumption, which differ in the absence of presence of collective synchronization in the process of transducing the quanta of ATP energy into biological work. For example, the synchronization of energy consumption in the form of muscle contraction occurs via the actin-myosin complex of thin and thick protein fibers. Without such synchronization, no effective force generation can be produced. Muscle deterioration associated with energy demonstrates how entropy increase leads to the loss of function. Similarly, the glycolytic switch associated with upregulated glycolytic mode of ATP production in cancer cells used to enable uncontrolled and unsynchronized cell division is an example of the classical mode of energy consumption.

The phenomenon called quantum de-coherence occurs in the case of mitochondrial disease is associated with the loss of quantum metabolism and a transition to the classical mode of energy production caused by the inflammatory cascades and oxidative stress, which are biologically equivalent to the increase of thermodynamic entropy and heat production. Heat is coupled with an increased concentration of reactive oxygen species that cause uncoupling of proteins, or to angiogenesis caused by inflammatory cytokines, or to inflammation resulting from the parallel upregulation of oxidative stress and oxidatively-modified constituents of mitochondria that impair mitochondrial function. Insulin resistance results from pro-inflammatory

cytokines that compromise mitochondrial function promoting heat and oxidative stress. Chronic and subclinical system-wide inflammation is an example of thermodynamic entropy generation in a biological system. It represents insidious degradation of biological complexity that correlates with the progression of disease states and the onset of senescence. In the setting of insulin resistance, a loss of physiological information and increasing compartmentalization accompanying thermodynamic entropy increase can be mediated by the following aspects: (a) increased neuro-humeral tone, i.e. increased sympathetic to parasympathetic autonomic nervous system balance, (b) disturbed gut microbiome, (c) disruption of insulin signaling in metabolic tissues and (d) high circulating insulin levels and (e) adipocyte derived inflammatory mediators and hormones.

The implications of quantum biology for future clinical applications are immense and so far largely unexplored. It might be possible to manipulate the biological wave function superpositions across the metabolic networks of human physiology to yield the most efficient solutions in order to achieve a state of optimal health under the set of prevailing conditions. This could even apply to conscious thought and cognitive process since it is well-known that a mind-body connection is a very powerful factor determining health and disease. The central axes of hermetic neuroendocrine and immune responses that are maximally adaptive, modulate oxidative and inflammatory responses so that chronic disease states are most favorably modified at the epigenetic level. The epigenetic environment favors the expression of genes for weight set-points, which are affected by the effects of bile acid metabolism, endogenous gut hormone GLP-1 and the gut microbiome. All these effects are regulated in complex nonlinear way, such that the outcome of these interacting factors in terms of obesity and metabolic disease states, e.g. diabetes. We believe that quantum algorithms may be used in the future to prevent the development of cancers and other diseases.

There also exists a real potential for biophotons to underpin synchronized coherent processes taking place in cell. This may be related to the interactions between mitochondria and microtubules. Further, mitochondria-derived biophotons interacting with microtubules can correlate with the functioning of the cell as a whole, for example affecting the strength of electrical α wave activity in the brain. As stated above, quantum decoherence is caused by heat generation. In biological systems, heat is released by reactive oxygen species generation and their recombination which is linked to inflammation. In mitochondria, reactive oxygen species cause up-regulation of uncoupling proteins in adipose tissue. There is a growing body of evidence that the molecular machinery of living cells involves emission and absorption of photons. Reports have been published indicating that biophotons participate in intra- and possibly inter-cellular communication [21]. They are usually emitted at a very low rate of 10/sec/cm^2 in cell culture. Mayburov [21] reported observation of biophoton clusters consisting of short almost-periodic bursts, which are very similar to binary data transmitted over a noisy channel. That could elucidate why cells detect low levels of electromagnetic radiation in a noisy environment. Biophoton absorption opens new exciting avenues for clinical applications in medicine, which could be coined photo-medicine. While the scientific literature on photobiomodulation (PBM) is relatively small, it has been steadily growing. It applies specific frequencies of electromagnetic spectrum that have been shown to lead to clinical benefits, for example in neurodegenerative diseases and cancer. PBM therapy with infrared light has been shown [22] to lead to substantial clinical benefits in clinical trials for dementia. Clinical benefits of light-level PBM have also been seen in the therapy for cancer, which uses red light with a wavelength of 670 nm and intensity of approximately 5 J/cm^2 [23]. One of the possible mechanisms here is enhanced oxidative phosphorylation in mitochondria [24], which would link it directly with the discussed theory of quantum metabolism.

Synchronization of Cellular Activities

The quantum superposition of wave functions and their quantum entanglement represent a metaphor for the synchronization of cells, tissues and organ systems throughout a healthy body. These phenomena occur in synchrony as an organismic whole. The transfer of electrons extracted from the breakdown of fatty acids and glucose into the electron transport chain of the mitochondrial TCA cycle is where this quantum effect may be taking place in living cells. Molecular biochemistry describes this electron transfer along the inner mitochondrial membrane showing how it then leads to a transfer of electrons along an electric potential gradient generated by the coupling of redox cycling enzymes. The final acceptor of electrons is oxygen, which combines with hydrogen protons to form water molecules. The energy produced in this process is used to form high-energy phosphate bonds when the conversion of ADP into ATP occurs. The relevance of this quantum phenomenon is manifested by the efficiency and synchronization of cellular metabolism. This may have been achieved in the process of evolution on this planet as a result of a retained evolutionary advantage provided by the efficiency of quantum mechanical processes. It is specifically illustrated by the clear advantage of mitochondrial ATP production (OxPhos) via the quantum mode compared to glycolysis, which is classical. Glycolysis involves chemical kinetics combined with Brownian motion of the reactants and products in the cytoplasm.

Two strategies can be adopted to achieve maximal metabolic efficiency, i.e either by synchronized coordination of quantum molecules for a coherent larger-scale effect, or by using a divergent superposition wave function encompassing a broad range of possible states. Using the former, it biophotons that originate from recombination of reactive oxygen species can mediate synchronization across the electron transport chains within and between the mitochondria of the same cell and even across different cells. Using latter, a broad superposition of various wave functions forms a quantum state, which allows the system to explore the range of possible outcomes via a quantum search algorithm that leads to a collapse on the most favorable state. This can also be at play in protein folding processes, DNA packaging and even genetic evolution where the search and retention of most favorable mutations can lead to advantageous properties. There may also be synchronization by interactions with the lattice vibrations of mitochondrial walls that could affect the electronic transitions within the protein complexes of the electron transfer chain. This may lead to the coordination of enzymatic activity of the TCA cycle enzymes that feed electrons into the electron transport chain.

Fröhlich [25] hypothesized that vibrations of phospholipid head groups in cellular membranes exhibit Bose-Einstein condensation, whereby dipolar oscillation quanta occupy a single quantum state leading to long-range coherence, net polarization of the cell and resonant attraction to similar cells. Fröhlich theorized that non-linear coupling between membrane dipole oscillators, which is driven by thermal fluctuations and metabolic energy pumping could explain the system's transition from random oscillations to a single coherent

dipole mode. This would allow a cell or an organism to efficiently store electromagnetic energy, which could control biochemical reactions and synchronize cellular activities. Consequently, low-frequency electromagnetic radiation could affect biological function by changing the oscillation frequency of these dipole modes and also interacting with the spin of an unpaired electron in a free radical. It should be noted that free radicals play important roles in cell signaling in normal physiology but they can also promote oxidative stress by stealing electrons and exacerbate the process of inflammation. From the physics point of view the main parameters related to the membrane structure are their thickness, electric potential gradient across them, mechanical rigidity and dielectric permeability. Notably, there are differences in this regard between membranes of cells in health and disease. The head groups are hydrophilic, hence they are exposed to the aqueous environment, both the cytoplasm and the extra-cellular matrix. The phospholipid tails are hydrophobic and hence they do not possess electrostatic charges. The electrostatic potential difference typically amounts to between 70 and 120 mV (but can drop down to 20 mV or less in cancer cells) over a distance of 4 to 5 nm, which gives rise to very strong electric fields on the order of 10 million V/m. Therefore, dipolar oscillations occur in the $10^{11} – 10^{12}$ Hz frequency range and these waves propagate along the membrane according to Fröhlich. This oscillatory behavior of dipole moments in membrane could be sufficient to emit electromagnetic radiation similarly to an antenna transmitting a radio signal. Fröhlich condensation effect could lead to a strong signal, which would be very useful for cell-cell communication due to its narrow frequency range. Specific electromagnetic frequencies can, therefore, be used for molecular recognition processes, for example, to promote aggregation. It is plausible that enzymes generate specific frequencies corresponding to their function and hence can be regulated by specific-frequency electromagnetic waves. Examples of such effects are now in evidence. THz electromagnetic radiation have been seen to affect diffusion and aggregation of BSA proteins [26], lysozyme (where they cause conformational changes in the α-helix region) [27] and transcription factors [28]. Experiments conducted in a much lower range of frequencies between 100 and 200 kHz, demonstrated that microtubules absorb this electric field energy, becoming distorted causing defective function of mitotic spindles in dividing cells [29]. This technology is now used to treat brain cancer by an Israeli company, Novocure, Inc. Other publications report the presence of biological resonances in the GHz and MHz regions of the electromagnetic radiation spectrum [30]. Mapping these various resonant frequencies to structure and function will open a new avenue in medical research, which could be termed bio-electro-medicine, with hopes for revolutionary changes in the treatment of human diseases. This may also lead to direct interventions into metabolic diseases where resonant oscillator frequencies can be tuned to change the body's response. By changing the characteristic frequency of a cell or tissue one may either enhance or hinder its biological activity. The phenomenon of biophoton generation and utilization in biology promises many potential applications whose understanding is hoped to advance practices in healthcare and medicine.

In tumor cells, the so-called Warburg effect signals a metabolic shift away from oxidative phosphorylation and toward glycolysis which is correlated with a malignant transformation. Eventually, their mitochondria become de-correlated and much less energetically efficient. This may imply that cancer collapses a superposition of the wave function that is responsible for coherently synchronized mitochondria and hence the efficiency of metabolic activity working in unison becomes degraded in correlation with the level of malignancy and then destroyed.

Another example of the importance of quantum concepts in medicine involves diabetes, where decrease of biophoton emission is related to loss of mitochondrial structure and function, which is known to occur in diabetes mellitus. This occurs in both forms of diabetes related to high levels of glucose feeding into the mitochondrial electron transport chain. Furthermore, in type 2 diabetes insulin resistance serves as an independent cause of mitochondrial disease the dependence of living systems on mitochondria and the involvement of quantum mechanics at a fundamental level leads to the conclusion that organismic life can be viewed as a quantum mechanical biological engine. In human physiology, roughly 60% of the energy released from the hydrolysis of ATP produces metabolic heat, which is not utilized for useful purposes of work. The mitochondrial way of producing energy is not only very efficient but well-engineered and requires a structure, unlike glycolysis where basically all the reagents are in the cytoplasm and react due to their affinities in a diffusion-limited way without any synchronization. Loss of metabolic coherence is usually associated with pathological transformations. Hence, disease states can be viewed as quantum decoherence phenomena. In particular, the loss of quantum coherence in cancer has been recently proposed [30].

Since ATP hydrolysis provides the energy needed to maintain the body's structure and function, it is important to understand the role of extracting energy from the information contained in nutrients. For example, muscle contraction is possible due to the establishment of an electrochemical potential across the myofibrils of actin and myosin by ATP hydrolysis. This is also needed for the mechanical sliding motion whereby myosin fibrils pull AFs inward and produce the contraction. ATP is required for the active transport process that generates the hyperpolarized electrochemical potential of all cells in the body. In neurons, electrical transmission is the mode of cell communication with other neurons or other types of cells. In endocrine cells such as the pancreas, it is important for insulin release. Electrical potential of cells provides a protective mechanism that keeps harmful molecules outside the cell. ATP hydrolysis also provides the energy necessary for many biosynthetic processes such as glucose phosphorylation. It provides the necessary activation energy for the rate-limiting step of phosphofructokinase.

DNA, hormones and kinases/phosphatases are sources of structural information that act as functional messengers. Some of these messengers operate within a cell (e.g. DNA) and some others across the cell membrane by communicating with the surroundings (e.g. extracellular hormones). However, intracellular hormones may interact with transcription factors that bind to DNA response elements. In this case, the extracellular hormone (e.g. cortisol) is the message, the DNA the messenger and effects such as vasoconstriction or bronchodilation can be viewed as the instruction output. The sequence of the integration in the information processing from the message to instructional output may be recognized in the context of the stress response and the psycho-neuro-endocrine-immune systems. Notably, the majority of the immune system is located in the wall of the gut (gastrointestinal associated lymphoid tissue or GALT). Another type of messaging system involves external agents that may penetrate into the human body and affect its functioning both negatively. As a case in point, the gastrointestinal tract is the primary portal of exposure to pathogenic microbes, toxins and allergens that mediate disease but they may also be necessary for the healthy functioning of the digestive system.

Metabolic diseases of aging, such as cancer, heart and vascular disease, Alzheimer's disease and accelerated cognitive decline, strongly correlate with the severity of mitochondrial dysfunction. In addition to pathogenic structural modifications induced by redox stress, the loss of mitochondrial function may be the result of other disturbed elements of systems biology that occur during the aging process. These may include inadequate oxygen supply, mitochondrial enzymes or cofactors. Altered composition of intestinal microbiota for instance, is often a critical perturbation resulting in dysfunctional mitochondria.

Motor protein functions requires ATP hydrolysis and accordingly impaired motor protein function such as myosin leads to reduced strength of muscle contraction. Thus, in addition to reduced muscle mass, muscle weakness is also present. Notably, all motion within the cell is driven by molecular motors including the spatial arrangement of mitochondria transported along microtubules and actin cytoskeleton, chromosome segregation via microtubule shortening which are attached by kinetochores in the process of mitosis, etc. Disturbances to these motions may perturb quantum metabolism and predispose cells to a transition to the cancerous phenotype.

Quantum Information and Nutrients

Informational energy provides useful work for a protein or a hormone that ultimately helps maintain homeostasis of glucose within the whole organism. Information flow occurs in both directions: bottom-up that is from proteins to cells to tissues, and top down, from organism to tissues to cells, e.g. in terms of nutrient and oxygen distribution. In living cells, information processing is mediated by cell membranes, which allow an external signal to be sent into the cell through membrane receptors relaying messages and providing instruction for a particular cellular transformation. For example, insulin binds to insulin receptors promoting autophosphorylation of the insulin receptor, which exemplifies structural information that upon insulin binding causes dynamical rearrangement representing functional information when contained in the message. This shows how information processing translates extracellular messages into the cell through cell membranes. However, intracellular steroid hormones bind to their receptors present within the cells. The bound receptor may interact with transcription factors that in turn bind to DNA response elements. In this case the hormone, e.g. cortisol, is the message, or the cortisol receptor contains structural information. Once bound to cortisol the information content of the cortisol receptor changes resulting in dynamical rearrangement of this structural information, that then triggers functional information responsible for transfer from the cytoplasm into the nucleus and binding to the DNA's cortisol response element. Therefore, transcription of anti-inflammatory cytokines within immune cells may be suppressed while pro-inflammatory cytokine transcription is activated. Information content may be based on quantum mechanics via a statistical relationship with macroscopic collective modes of the interacting elements. Quantum information theory differs from classical information theory, mainly because of the difference between the qubit and an ordinary bit. A qubit provides a much greater information capacity due to its complex number definition as opposed to a binary (0 or 1) content of the classical bit. Hence it has a greater ability to find a biologically most efficient solution for an optimization problem. It can be represented by a divergent complex wave function that covers an increasing combinatorial space allowing the system to rapidly explore many different states of this space. Hence, quantum search algorithms provide huge speed-ups and improved efficiency. On the other hand, quantum coherence provides the ability to coordinate and synchronize behavior of constituent parts of a system over spatial domains, offering a functional advantage. Note that wave functions left to themselves spread out over time due to decoherence, losing their information content because asymptotically the quantum wave function has the same probability everywhere. However, signal amplification if implemented in the system, can refresh the information content of a wave function resulting in its convergence. The ultimate convergence of a wave function is its collapse in the process of taking a measurement and forcing the quantum system to "declare" its state and provide a measurable value to the experimenter. Quantum entanglement is a mechanism that can overcome the energetic cost of information processing. When two quantum systems are entangled, they form a composite state. Entanglement allows us to see the whole but not isolate one component from another. Quantum entanglement, therefore, provides a connection between the system and its constituents.

The process of senescence represents a progression towards greater entropy and reduced local organization of structure and function. Since negative entropy represents information, senescence results in the loss of biological information over time due to both natural and pathological degradation processes. Since it takes energy to break chemical bonds, and since heat is thermal energy, which is abundant in a living system, heat can be seen as facilitating bond breaking. In the case of dietary fuel, oxygen, concentration gradients of products and reactants, vitamins, minerals and phytonutrients, and enzymes are all required for biological purposes. The extraction of energy as heat and ultimate translation of information into work requires all the correctly balanced components of information to be present. Proper formation of structures constructed to be able to perform biological functions contains an enormous amount of information, i.e. negative entropy. Breaking bonds and degrading biological structure is an incineration process, which is accelerated by excess heat. This is typically an outcome of chronic inflammation and oxidative stress, which disrupt the information flow and information retention leading to an entropy increase. The decoupling and separation of energy from information is a process that proceeds in parallel with disease progression and senescence that characterize the transition from life to death. However, energy is also needed to sustain and repair damaged structure, which becomes degraded by both natural processes and accidental injury. Hence, proper flow of both information and energy is the key. One might say that the secret to any properly functioning relationship is exchange of energy and information. This applies to living cells as much as to human beings and even societies.

Quantum Medicine and the Defense against Biological Aging

Prolonged vitamin D deficiency seems to fundamentally predispose to an altered microbiome due to an essential role that vitamin D plays in regulating the innate immune system. Conversely, insufficient nutrient composition in the diet, which although influences the gut microbiome, represents an epigenetic modulator of the host gene and microbiome expression due to a lack of necessary enzyme cofactors. Such micronutrient cofactors are necessary for bioenergetic pathways and, as a result, the input of energy accompanying a specific assortment of reactants determines the ability to extract energy from the dietary nutrient supply. This energy extraction process is dependent on all the reactants and products in the metabolic systems rather than one or few of the reactants. This powerfully reflects the

complexities of the human body. The energy flows are correlated with the information present in the molecular machinery of the cell. However, this transformation of information does also require an adequate expenditure of energy in the form of work. Hence, converting heat to internal energy can, in turn, create an enduring well-functioning structure.

Expenditure of energy in the form of work is needed to overcome a natural tendency of entropy production through degradation of structural complexity. Many people who live to be 100+ years old are both physically and mentally active, which can be viewed as an adaptive hormesis with an optimal stress response activation. This supports the hypothesis that the extent of staying in quantum metabolic states is correlated with health since quantum metabolic regime corresponds to minimized entropy production. Utilizing quantum metabolism eliminates excess entropy by expending energy through the work of performing useful cognitive and physical processes. In the physiological energy balance equation, both input and output count. Input is in the form of nutrition and information, while output occurs as heat dissipation and work. It is important to note that entropy can be lowered by increasing information. Hence, one way of overcoming the damage due to aging can be to keep learning as it increases information content not only in our brain but also in other organs of the human body. Being physically active removes excess stores of nutritional energy that can otherwise be transformed into destructive heat dissipation or structural degradation. Additionally, the less classical manifestations of micronutrient deficiencies are related to information degradation. For example, obesity, cancer, cardiovascular disease, Alzheimer's disease and accelerated cognitive decline can be described by increased entropy production. The following are some classical disease states of micronutrient deficiencies: Vitamin A (retinol) to xeroethalma (night blindness); Vitamin C (ascorbic acid) to scurvy; Vitamin D (calciferol) to rickets; Vitamin B_1 (thiamin) to beriberi; and Vitamin B_3 (niacin) possibly to pellagra. Vitamin B1 (Thiamin) classically leads to beriberi. Other classical mineral deficiencies include those of iron and iodine and lead to anemia and thyroid goiter, respectively. In addition, chronic disease states of aging, such as Alzheimer's disease, accelerated cognitive decline, cancers and cardiovascular disease are a function of mitochondrial dysfunction and often insulin resistance.

Twenty-one kinds of minerals are required for proper mitochondrial function, making efficient energy production possible. In addition to minerals, such as magnesium, zinc, selenium and many others, vitamins and other antioxidants, amino acids and fatty acids feed into the TCA cycle and electron transport chain of oxidative phosphorylation leading to optimal ATP production. For example, the amino acids cysteine, glutamine and glycine together make glutathione, the major antioxidant of the body to manage oxidative stress, preventing excess oxidative damage. The electron transport chain is the most common source of oxidative stress often due to energy overload providing electrons into the electron transport chain. This is often found in persons with dietary excess and obesity. It is plausible that insulin resistance, which prevents the decarboxylation of pyruvate to acetyl CoA in the mitochondria for further oxidative metabolism represents a protective mechanism to prevent a pernicious feed-forward process. a-Lipoic acid is an important antioxidant necessary for optimal mitochondrial function. Coenzyme Q_{10} is necessary for electron transfer within the electron transport chain. Carnitine, a trimethylated amino acid that may be produced by *de novo* biosynthesis utilizing lysine and methionine, is required for oxidation of fats allowing acetyl CoA to feed into the TCA cycle [31]. Carnitine may also be derived from exogenous sources such as red meat, fish and dairy products. The AC:FC (acylated carnitine: free carnitine) ratio is a useful metric for assessing carnitine availability and mitochondrial function or energy production. An increased value of this ratio points to carnitine deficiency and reduced mitochondrial function. Conversely a low AC:FC ratio suggests healthy mitochondrial function and adequate carnitine availability. Evidence shows that reduced carnitine is associated with mitochondrial dysfunction [32]. This may play a role in the loss of nitric oxide signaling and development of endothelial dysfunction associated with cardiovascular diseases [33].

The stripping of bio-nutrients as a result of over-consumption of white flour, white sugar, white rice or white wine represents the loss of information since it correlates with a decrease in biological organizational complexity. Hence, excessive intake of a nutrient-poor diet causes useless energy to be broadly deposited as adipose stores. Without nutrient informational energy the deficient minerals and vitamins are unable to serve as cofactors that catalyze enzymes of the bioenergetic pathways and metabolic reactions. Moreover, the lack of phytonutrients decreases antioxidant effects. Conversely, a phytonutrient rich diet and robust antioxidant response promote the flow of free energy that reorganizes and revitalizes the body's biochemistry while reducing the entropy increase. Notably, obesity is itself promoted by an informationally depleted diet, e.g. phytonutrient-deficient diet, whose consequence is lipid accumulation within adipocytes, which outgrows the blood supply. This causes an inflammatory process when the lipid outstrips its blood supply within the adipocyte. Informationally-rich nutrition is characterized by a high ratio of muscle mass to fat. Conversely, an informationally-depleted diet with high energy content typically promotes sarcopenic obesity. Pathophysiological nutrient depletion leads to mitochondrial dysfunction and relative lack of ATP generation in mitochondria. This results in insulin resistance, which impairs the satiety centers of the brain to a greater extent that it does the enzyme lipoprotein lipase responsible for the uptake of circulating triglycerides and storage in fat tissues. To maintain body temperature, the human body needs a steady supply of simple foods that can be easily metabolized, for example glucose, fructose, etc. However, for the complex functionality of enzymes our bodies also need micronutrients, which carry a high information content. These molecules are needed in specific locations, hence high information content due to their functional specificity, which is both spatial and temporal. Optimal structure and function of enzymes enables their cyclicity of action that is optimal for physiologic needs of the organism. Particular mineral and vitamin cofactors are needed for the catalysis of the enzymatic activity. Quantum metabolism is a mechanism that ensures this in a spatially and temporally correlated way. The protein enzyme complexes of the electron transport chain function as quantum harmonic oscillators whose oscillations are correlated with the quantity of nutrient consumed. As nutrient bio-fuel intake increases, more and more metabolic enzymes including the glycolytic enzymes, become activated. It is conceivable that at lower level of nutrient supply, nutrient concentrations correlate linearly with enzyme activation, giving rise to quantum harmonic oscillations characterized by a high level of efficiency. However, glycolysis is driven by Brownian diffusion of the substrates and products in the sequence that ultimately produces pyruvate that enters the mitochondria. From there the cyclical pathway of the TCA cycle produces the NADH and $FADH_2$ that is brought to the electron transport chain complexes 1 and 2, respectively. In addition, fatty acids undergo fatty acid oxidation

producing acetyl CoA that combines with oxaloacetate that produces citrate in the initial step of that cyclical pathway. Finally, amino acids feed in at various substrate levels of the TCA cycle. Hence, the only component of the metabolic production of ATP that represents a quantum harmonic oscillator is the electron transport chain. In this case, there is no excessive degree of electron leakage along the inner mitochondrial membrane. Conversely, when macronutrient consumption is excessive such that the amount of NADH and $FADH_2$ feeding into the electron transport chain surpasses the take-over threshold, the quantum harmonic oscillators of the electron transport chain across mitochondria become de-correlated and hence cellular metabolism functions in the classical regime, which is vastly less efficient.

According to the Warburg effect which is a hallmark of cancer cells, an increasing amount of energy production is carried out using the glycolytic pathway at the expense of OxPhos. This glycolytic shift correlates with the stage of malignancy and progression of the disease. As this happens, cancer cells become desynchronized from one another and from the host tissue or organ. The "take-over threshold" defined by quantum metabolism theory represents the nutrient level above which electron leaking takes place, along with the formation of reactive oxygen species and inflammation resulting in the disruption of mitochondrial structure and function. Although ATP is a quantized metabolic energy unit, the process of metabolism involves numerous biochemical pathways in a multitude of cells. As a consequence, depending on the dimensionality and the characteristic turnover times, different allometric scaling laws emerge from statistical averaging, including a phase transition to the classical limit if the nutrient supply exceeds a critical value.

A person may be depleting the body of valuable nutrients and causing weight gain due to poorly metabolized food, i.e. not converting food catabolism into the energy currency of ATP, or because of an unbalanced diet. An opposite tendency may drive a person toward a constant weight loss (cachexia) resulting from other issues, for example tumor growth with its glycolytic metabolism or inadequate energy supply, respectively. There is also the gradual change in the metabolic rates with aging as well as resulting from psychosomatic factors (e.g. anorexia nervosa or stress-driven overeating). Additionally, changes in microbiome can cause increased energy extraction (depletion of the microbiome) with associated weight gain or conversely, a repletion of the microbiome causing a decreased energy extraction and weight loss [34].

Relevance of Quantum Biology to Health and Disease

The field of quantum biology has been launched by recognizing the quantum nature of photosynthesis and mitochondria, the functioning of metabolic enzymes in the mitochondria, and the allometric scaling laws of physiology. The theory of quantum metabolism demonstrates mathematically that basal metabolic rate is a function of size, especially in optimally functioning healthy cells. When pathological states set in, a problem emerges that can be understood within the context of decoherence and desynchronization. In particular, inflammation and oxidative stress are the driving forces of clinical disease that starts at a subclinical level but then progresses to the feed-forward culmination of fully-developed disease states. The process of disease progression is promiscuous since it is independent of the type of tissue or organ system involved. Hence, the current healthcare model of compartmentalized and sub-specialized medicine is too narrowly focused and should be revisited. Quantum biology offers a new perspective for understanding disease, which could provide an improved potential for both preventing disease and treating it. The breakdown for quantum metabolism appears largely rooted in mitochondria and their energy producing networks with super-physiologic levels of oxidative stress and heat generation associated with inflammation. This is typically initiated and sustained by dietary excess relative to physiological requirements whereby too many electrons overburden the electron transport chain. Many of these electrons leak and are scavenged by oxygen molecules to form superoxides and free radicals. This leads to the generation of the NFkB complex leading to and inflammatory response that causes loss of mitochondrial structure and function. This, by linking it to the Warburg Effect, sheds light on the association between diabetes and cancer, the latter by impairing nutrient metabolism and providing selective advantage to cancer cells, which favor glycolysis for the energy needs of cell replication and hence outcompete normal cells.

Mitochondrial dysfunction also figures prominently in the etiology of all chronic diseases of aging and is fundamentally related to insulin resistance and to neurodegenerative processes of accelerated cognitive decline and Alzheimer's disease. Importantly in this connection, glycolytic metabolism is characterized by lower energetic efficiency, which physiologically translates into reduced biological complexity with broken interconnectedness. Therefore, cancer cells become uncorrelated from the host tissue and from other cancer cells with insufficient energy to perform functional differentiation but enough energy for cell division. Normal tissues that are overburdened with excessive dietary consumption are characterized by impaired mitochondrial structure and function due to oxidative stress and inflammation. The consequence of it may give rise to the Warburg Effect with the anaplerotic process of using mitochondrial substrates for the reproductive, which can cause cancer initiation.

Insulin resistance which is the root cause of type 2 diabetes exhibits an increase in pyruvate kinase with reduced pyruvate dehydrogenase enzyme complex. Insulin resistance and type 2 diabetes represent the classic metabolic disease states characterized by a transition from quantum metabolism to a classical regimen of energy transduction. This results in a reduced metabolic rate with less ATP being produced per unit nutrient of glucose per unit time. The amount of energy production of ATP in mitochondria from one mole of glucose ranges from 32 to 34 moles in contrast to only 2 moles produced from glycolysis. This transition takes place when the mitochondrial capacity for energy production is exceeded by nutrient supply,

The healthy human central nervous system maintains coherence throughout the body using downstream signaling which is transmitted through the neuroendocrine system, the autonomic and peripheral nervous systems across all cells of the body. We propose that the whole-body coherence functions in the quantum regime. This is supported by the virtually instantaneous time from visual stimuli in the retina of the eyes to the acral extremities, which cannot be explained by nerve conduction times or classical models of physiology. Cognitions generated in the central nervous system may be propagating synchronously utilizing long-range coherence with distant body parts, both in an autonomic manner mediated by the neuroendocrine and nervous systems. Therefore, classical physiology mechanisms should be augmented by quantum metabolism, especially involving long-range correlated bioenergetics. These mechanisms may be spatially and temporally correlated *via* the energy supply from ATP hydrolysis

to satisfy the energetic demands of neural, and neuroendocrine functioning. It is also intriguing to invoke organized structured water, both intracellular and extracellular, since it can facilitate ultrafast electromagnetic signal propagation, which is much faster than the consecutive synapsing relay of neural transmission. This would allow virtually simultaneous transmission of signals between disparate parts of the body and their organism-wide synchronization. Additional examples illustrating that electromagnetic energy produces electronically excited states, which correlate with essential biochemical processes required for metabolic health in the human body are given below. Melanin in the skin is a chromophore, which absorbs sunlight to produce vitamin D. This is very analogous to the heterocyclic aromatic rings, chlorins. Magnesium containing chlorins are called chlorophyll, the central photosensitive pigment in chloroplasts of plants. In both cases a certain wavelength of light is absorbed by the chromophore by exciting an electron from its ground state into an excited state. Conjugated chromophoric molecules have alternating single and double bonds creating the delocalized excited electron state between energy levels extended along orbitals. Vitamin D is associated with significant salutary effects on the primarily innate immune system, which have been correlated with reduced risk of breast, colorectal and other cancers. For example, leukemic cells bathed in vitamin D solutions turn normal [35]. Vitamin D is also associated with reduced risks of cardiovascular disease, diabetes, obesity and neurodegenerative diseases. Using high doses of vitamin D at the onset of type 1 diabetes, schizophrenia, Graves' disease or inflammatory bowel disease, has been reported to result in therapeutic remission in many patients. Moreover, lymphoma cells bathed in vitamin D solution have been shown to revert to their normal state [30]. Recent studies have demonstrated that vitamin D reduces the progression from pre-diabetes to diabetes. It is worth considering vitamin D in the context of photon absorption by melanin, which is analogous to aromatic porphyrin rings in cytochrome oxidase of mitochondria, richly endowed in the cells of the innate immune system due to their high energetic demands or in hemoglobin. Clearly, electromagnetic effects of sunlight have physiological significance.

A Quantum Medicine Perspective of Energy and Information Flow in Health and Disease

The emerging field of quantum medicine may play an important role in providing an integrative view of entanglement between cells in the human body. In the absence of quantum biology insights, it is hard, if not impossible to generate an integrated representation of the physiological whole because reactants and products of biochemical processes are often intricately entangled. There is also entanglement of energy in the systems biology of the human organism, which includes long-range coherence, driven by nutritional energy supply.

To translate these observations into clinical practice, it is intriguing that quantum mechanisms may explain the placebo effect. Patients on blinded clinical trials are not informed if they are given a real drug or are on a placebo pill, which may affect their body's response since in their minds there is a superposition of both possibilities present and can with some probability elicit an effect. Similarly, the power of a positive belief system is hence conceptually rooted in quantum theory.

In the context of disease, the complex interactions within systems biology may lead to a break-down of coherence in a pathological state whereby individual systems with the overall system become isolated and compartmentalized. This may also cause an increase of the thermodynamic entropy and hence result in senescence. Clearly, explaining, especially in quantitative terms, the coordination of the organism as a whole is a major challenge in the field of biology. Communication, interactions and signal propagation in the human body are commonly thought to include electrical signaling by the central and peripheral nervous systems, chemical signaling through blood flow with hormones and cytokines. Moreover, inter- and intra-cellular connections in the body, which form a structurally and mechanically connected link between the cytoskeleton, the nuclei of cells, and the extracellular matrix indicate the possibility for mechanical transduction in addition to the traditional chemical and biochemical signaling. Intra-cellular polymeric structures involving microtubules, AFs, and collagen have been considered as bio-nanowires that form a mechanical tensegrity matrix throughout the body; in addition to their structural roles, they are potentially capable of high-speed electrical, protonic, ionic and possibly electronic signaling. Bioelectrical signaling is known to be involved in regeneration and functional ordering of the organism. Non-chemical information processing and propagation may include not only electrons, ions, and protons but also excitons and other types of quantum quasiparticles such as polarons, phonons and magnons. Integration of these signals should involve hierarchical organization over spatial and temporal scales where the faster processes affect the slower ones.

Also, still unclear but emerging as playing an important role in the above processes is the function of structured water in the propagation of biological signals due to its organization imparted by hydrophilic surfaces. This, so-called fourth phase of water, is characterized by long-range spatial correlations, which lower the amount of thermal fluctuations and hence enhance electric signal due to a lower dielectric constant, dipole ordering and protonic conduction. Experimental evidence for protonic conduction in water that surrounds proteins exists in the literature. This has been found for example for collagen, keratin, cytochrome c and hemoglobin. Protonic conduction involves hydronium water structures, which surround proteins, and is different from electronic tunneling due to the shorter distances traveled by individual protons and a tightly organized water environment [6]. Much more needs to be investigated to understand the profound influence of biological water on the functioning of biopolymers and cells as a whole, importantly including their quantum degrees of freedom.

Conclusion

The relevance of the insights presented in this paper to clinical medicine and healthcare is multifold. First, it allows patients to help themselves by better understanding the perspectives of energy flow in the human organism. It also promises to advance the diagnostic and therapeutic approaches based on metabolic mechanisms involved in health and disease. Living systems have been presented in this paper as quantum coherent when in a state of health. Therefore, disturbing the delicate balance may have consequences, such as diseases including cancer [36] whose physical origin is hypothesized to be a disturbance of quantum coherence at the cell level. For example, this gives pathophysiological context of burnout. It also gives context to how healthy lifestyles (diet, sleep, activity, mindful meditation and yoga) prolong life and health spans. This perspective also leads to a conclusion that toxic and vitalizing stress cannot be present at the same time, somewhat similarly to two complementary quantum variables that cannot be simultaneously measured. Hence, healthy lifestyles protect us from toxic stress that steals from us the emotional IQ, the love,

empathy, the intuitions and the awareness of awareness that defines our consciousness. Vitalizing stress empowers human connection and networking, as collective intelligence that makes it possible to maintain personal expectations over time, which indeed results in fulfillment and happiness. On the other hand, toxic stress in one of its forms (i.e. cortisol-driven, which acts on the amygdala) relates to fear. Anger is rooted in fear, and chronic fear, which is always imaginary, not real, leads to anxiety, depression and chronic disease. Depression has a 30% increased risk of a MI and a 36% increased risk of CV mortality. A second form of toxic stress is a consequence of the first, or burnout; whereby cortisol resistance is due to Brain-Derived Neurotrophic Factor (BDNF) phosphorylation, which exhibits negative correlation with cortisol. Cortisol promotes transcription of energy producing machinery carried out in the mitochondria (hence direct correlation with quantum metabolism), which explains physical, mental and emotional exhaustion. The end result is a mental state with no fear of giving up, whose consequence is suicide, divorce, drug and alcohol addictions. This underscores the importance of healthy diet, sleep and physical activity, hence we do need to take heed of the importance of taking breaks and vacations from work, mindful meditation and yoga which prevent toxic stress, all of which slow down the progression of the chronic diseases of aging, and promote the joys of life.

Vitalizing stress is what competent medical professionals do when providing psychological support to patients, other healthcare providers and even hospital administrations. While change is an inescapable hallmark of time, and fear often associates with change, human connection and networking, a collective intelligence, makes it easier to undergo changes in life. In both physiology and society, integration is a hallmark of health while isolation is characteristic of disease. Thus, physiological purpose is inspiring by being motivated to survive not only as individuals, but to help others do so as well, by promoting the joys, opportunities, health and general welfare of others. This then is the intrinsic reward and the privilege of the life service in a medical profession. Nothing is more elevating than to become part of a new system-wide whole that is greater than the sum of its parts. The field of modern medicine should be further developed to include the totality of a human person, both the physical aspects including the latest discoveries in the areas of systems biology, molecular biology, quantum biology, etc. but also the intangible aspects of human behavior that continue to amaze and inspire us to achieve our full human potential.

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