Chapter

The Effect of Repeated Electromagnetic Fields Stimulation in Biological Systems

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Abstract

The effects of electromagnetic fields on living organs have been explored with the use of both biological experimentation and computer simulations. In this paper we will examine the effects of the repeated electromagnetic field stimulation (REMFS) on cell cultures, mouse models, and computer simulations for diagnostic purposes. In our biological experiments we used 50 MHz and 64 MHz since this is approved in MRI systems. REMFS upregulated pathways that control the aging process such as proteostasis. REMFS delayed and reversed cellular senescence in mouse and human cell cultures. More recently we determined that REMFS decreases toxic protein beta amyloid levels, which is the cause of Alzheimer's disease (AD), in human neuronal cultures. The mechanism of these effects is the reactivation of the heat shock factor 1 (HSF1). HSF1 activation is a quantum effect of the EMF-oscillations on the water that surrounds a long non-coding RNA, allowing it to then bind and activate the HSF1. We also performed electromagnetic (EM) computer simulations of virtual prototypes of bone cancer, femur fracture, and diabetic foot ulcers utilizing different frequencies and power applications to build an accurate differential diagnosis. These applications indicate the feasibility of subsequent practical models for diagnosing and treating human diseases.

Keywords: electromagnetic, aging, Alzheimer's, simulation, diagnosis, treatment

1. Introduction

Living organisms interact with and adapt to the EMF environment. This discovery has ignited interest in the analysis of the EMF-biological systems [1–4]. Researchers imagine that precise tuning of experimental and clinical REMFS exposure could lead to favorable health results including the development of treatment and diagnostic devices [5, 6]. REMFS exposures produce the activation of multiple biological pathways, including changes in Ca^{2+} regulation [7, 8], channel activity [9], enzyme activity [10], RNA and DNA synthesis [11–13], expression of microRNA [14–16], free radical processes in the genetic effects of EMF [17–19], decreasing oxidative stress [20–24], activation of the heat shock response [25], activation of the heat shock factor 1 (HSF1) [26], cytoprotecting [27], growth behavior [11, 28], activation of the ubiquitin-proteasome [29–31], autophagy-lysosome systems [32],

inflammation [33–35], mitochondrial enhancement [36], neuronal activity [37], and a reduction in β-secretase activity [38].

Here, we will focus on studies performed on the REMFS spectrum (50–918 MHz) to explain the mechanism by which non-ionizing, non-thermal, non-modulated, continuous waves cause biological effects. We will use our and other researchers' recent results on human cell cultures and mouse AD models to explain this interaction. Initially, the frequency used in our REMFS experiments was 50 MHz with a specific absorption rate (SAR) of 0.5 W/kg. We found that these exposures upregulated the heat shock factor-1 (HSF1) in human lymphocytes and mouse fibroblasts [39]. HSF1 upregulation increased 70-kDa heat shock protein (HSP70) levels and delayed cellular senescence and death in these cell cultures [39]. Our recent data [40] demonstrated that cultures treated with REMFS at 64 MHz, with a SAR of 0.6 W/kg for 1 h daily for 21 days, had significantly reduced ($p = 0.001$) levels of Aβ40 peptide, compared to untreated cultures [40]. We also demonstrated a quantitative reduction of Aβ levels in primary human neuron cultures after different times and power protocols. There are further therapeutic implications of REMFS based on the improved cognitive function noted by lowering of Aβ levels in several AD mouse model studies performed by other investigators using 918 MHz exposures [36–38, 41].

The aforementioned biological effects demonstrate that REMFS is a multi-target strategy with potentially therapeutic implications on human diseases. In fact, among the biological effects observed, results of our experiments promote the capacity of REMFS to influence various networks of physiological functions that are dysregulated in the aging process and in Late Onset Alzheimer's disease (LOAD) [39, 40, 42].

2. Quantum mechanism of REMFS

The low energy (2–37 eV^{-7}) of the REMFS exposures is not able to cause any chemical change under the provision of classical physics, since the atoms or molecules pass through a potential barrier that they theoretically cannot overcome [43]. Our main challenge is to explain the mechanism of the REMFS-biological system interaction. There is a disparity between the low energy carried by the REMFS perturbation and the response of the biological system. The REMFS biological system interaction is a paradox from the classical point of view as it enables elementary particles and atoms to penetrate an energetic barrier without the need for sufficient energy to overcome it. To solve this paradox we have to look into the quantum scale and examine non-classical physical phenomenon such as wave-particle duality and quantum tunneling [44].

Despite this difficulty here we will describe a plausible sequence of events and a mathematical model for the REMFS-interaction. First we need to consider the REMFS perturbation as a time dependent adiabatic perturbation of water (the most likely receptor for REMFS), specifically the H bond network of the interfacial water [45]. REMFS subjects the quantum system, in the form of the H bond, to gradually changing external conditions giving the quantum system sufficient time for the functional form to adapt [46]. The probabilities of quantum transitions of the adiabatic change in the frequency of the quantum system have been calculated previously on the example of the harmonic oscillator [47].

The reason for the REMFS biological effects rests on the difference between the man-made EMF, and the natural EMF [48]. Man-made EMF waves are produced by parallel EMF oscillating circuits, whereas natural electromagnetic radiation is produced by atomic events such as nuclear fusion from the sun releasing infrared,

visible, ultraviolet, X-rays [48]. For this reason, man-made RF-EMF vibrations occur in a single plane, so they are polarized in contrast to the multi plane vibrations from the natural EMF waves. This polarization would explain the differences in the biological effects of man-made versus natural RF-EMF. The polarized RF-EMF exposure has the ability to force all charged/polar molecules and chemical bonds to oscillate on parallel planes, and in phase with the applied polarized field [48, 49]. This external excitatory oscillation forces the exposed physical or chemical system to vibrate at the excitatory frequency changing the frequency of the system to the excitatory frequency [50, 51]. One of the targets of this driven oscillation is the hydrogen bond (HB) network of the first layer of the interfacial water (FLIFW) that surrounds an RNA which in the case of REMFS is a long non-coding RNA (HSR1) [52, 53]. The REMFS oscillations are absorbed by the HB which then acts as a driven quantum harmonic oscillator [54]. This HB responds to REMFS increasing its vibration amplitude [55] with the consequent decreased distance in the direction of the nucleic acid [56]. Since the tunnel probability is proportional to the square of the amplitude, the tunneling probability is increased. REMFS induced quantum tunneling allows proton transfer from the interfacial water to the nucleic acids of RNA [57]. The protonation of the nucleic acid results in tautomeric interconversions [58] with the consequent conformational changes. In the case of the REMFS, a long non-coding RNA called Heat shock RNA (HSR1) changes from a close to an open structure [53] able to bind and activate HSF1 to initiate the expression of several heat shock proteins and chaperones including HSP70 [39].

3. REMFS mathematical model

We developed a mathematical model of the REMFS and biological systems interaction at the quantum level. We hypothesized the quantum effects of REMFS that explain how a low energy exposure is able to produce biochemical changes. For clarity, we divided them into 3 stages with the consequent three equations (see **Figure 1**).

Stage 1. The oscillating REMFS energy causes a time dependent adiabatic perturbation on the first layer of the interfacial water (FLIFW). REMFS perturbs the HB from FLIFW to the oxygen (O) of the "Guanine of the RNA" (GRNA). Under REMFS the H bond of the FLIFW acts as a driven quantum harmonic oscillator increasing the amplitude of the HB vibrations. The following equation estimates the increase in the amplitude of HB vibration when it acts as a driven quantum harmonic oscillator system under REMFS [59]. See following time dependent equation from Piilo et al. to find the amplitude change under REMFS:

$$F(t) = \frac{A\cos(\omega t + \varphi)}{\sqrt{2m\hbar\omega_0}} \tag{1.1}$$

We will obtain the change in the amplitude of the H bond vibration under REMFS:

$$A = \frac{F(t)\sqrt{2m\hbar\omega_0}}{\cos(\omega t + \varphi)} \tag{1.2}$$

Where A describes the amplitude and ω the oscillation frequency of the periodic force, ω_0 is the frequency of the oscillator, m is the mass of the oscillator, φ is the phase of the driving field, t is the time of the exposure, F(t) is the time dependent periodic force, and $\hbar$ is the reduced Planck's constant.

Stage 2. The increased HB vibration amplitude induced by REMFS triggers shortening of the HB of the FLIFW to O of the GRNA. The calculated distance

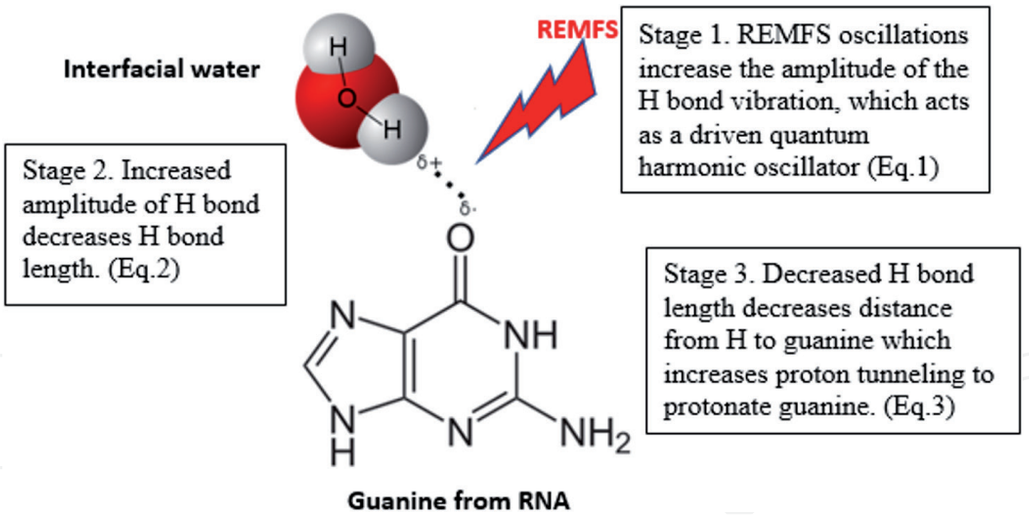

Figure 1.
REMFS quantum effects on the first layer of the interfacial water of the RNA. REMFS (repeated electromagnetic field stimulation).

between the H from the first layer of the interfacial water and the Oxygen of the RNA Oxygen is 1.85 Å [60]. This value is very short, predisposing the H for quantum tunneling. The following equation estimates the change in HB shortening as a function of the amplitude of the oscillation [61].

To find the variation of the HB distance we will use the equation from Samdal et al. using the average over the inter-nuclear configurations of the interfacial water and the RNA nucleic acids (r_a^{exp}) which is given as:

$$r_a^{exp} = \langle r \rangle = \int F_r(q)\, P(q)\, d\, q \tag{2.1}$$

$F_r(q)$ = variation of bond distance; $P(q)$ = probability function.

The equation of $P(q)$ in the classical Boltzmann approximation is:

$$P(q) = 1/N \int \exp\left(-\frac{V(q)}{RT}\right) dq \tag{2.2}$$

This equation predicts the shortening of the HB of the interfacial water under the time dependent perturbation caused by REMFS.

Stage 3. Shortening of the H bond decreases distance from the H from the FLIFW to the O from the GRNA. This will increase the probability of proton tunneling. The following equation estimates the quantum tunneling probability when barrier thickness or distance decreases [43].

$$-\frac{\hbar^2}{2m}\frac{d^2\Psi(x)}{dx^2} = (E - U_0)\Psi(x) \tag{3}$$

$\Psi = A\, e^{-\alpha x}$, where $\alpha = \sqrt{\frac{2m(U_0 - E)}{\hbar^{2.}}}$

Where E is a particle of energy, U_0 is the height of the barrier, and $E < U_0$. Also where m is the mass, d is the thickness of the barrier, α is the attenuation factor.

These three equations formed the mathematical model that is able to predict how the time dependent perturbation caused by REMFS affects the HB network of the first layer of the interfacial water. This HB acts as a quantum harmonic oscillator to produce proton tunneling and the protonation of the nucleic acids of the surrounding RNA to produce biological effects.

4. REMFS biological effects

4.1 REMFS effects in aging and age-related diseases

Multiple studies have found that repeated mild heat-shock (RMHS) produce beneficial effects on human fibroblasts experiencing in vitro senescence [62]. This prompted our laboratory to study the effects of a similar electromagnetic stimuli but instead applying lower frequency energy and therefore less risk of producing heat damage (430 THz vs. 64 MHz). The fact that the energy of the REMFS exposures are several orders of magnitude lower energy that heat exposure, yet both heat and REMFS are able to activate the HSR, makes REMFS a more suitable and safer strategy to activate this biological pathway to prevent and treat age-related diseases. We hypothesized that these exposures would produce anti-aging changes such as delay of in vitro senescence, would also lead to retardation of progressive cell enlargement, prevention of development of abnormal proteins, increased glutathione, and decrease in age-dependent glycosylation [63], as well as maintenance of youthful morphology, increased proteasome activity, increased levels of various heat shock proteins (HSP's), increased resistance against oxidative abilities, and UV-A irradiation similar to repeated mild heat shock [64]. Interestingly many of these anti-aging effects are produce by the heat shock response (HSR) elements [65]. In fact, attenuation in the HSR during senescence is the earliest event in the aging process, and is characterized by loss of proteostasis [66] that comes as a result of decreased heat shock factor-1 (HSF1) DNA-binding [67].

4.1.1 REMFS delays cellular senescence

Originally our laboratory utilized a frequency of 50 MHz, a power of 0.5 W, and a specific absorption rate (SAR) of 0.6 W/kg to expose different types of cell cultures applying different dose regimes [39]. REMFS treated cell cultures showed anti-aging effects. The proposed mechanism is the activation of HSF1 when REMFS releases HSF1 from its repressor Hsp90 to activate it. This study suggests that EMF exposure directly interacts with the HSF1-Hsp90 complex, releasing HSF1 for activation preparing it for following injuries. Our experiments also revealed that REMFS increased the population doublings number and changed the morphology of the cells to youthful appearance near the end of their replicative life in wild type, but not in the knockout HSF1 cell cultures. REMSF also decreased cell mortality in human T-cells. Remarkably, REMFS also increased HSF1 phosphorylation, enhanced HSF1-DNA binding, and improved HSP70 expression relative to non-treated cells [39].

We hypothesized a mechanism in which REMFS oscillation produces increase amplitude of the hydrogen bond of the interfacial water, therefore increasing the probability of proton tunneling. This proton transfer between the hydrogen bond of the interfacial water and the oxygen of the adjacent nucleic acids of the heat-shock-RNA1 (HSR1) will protonate the nucleic acid to form tautomers [58] that will cause conformational changes in this long non-coding RNA [68]. This secondary structure would be able to bind HSF1 and activate it by dissociation from the repressor chaperone HSP90 [39]. Then, activated HSF1 enters the nucleus and binds DNA to induce expression of beneficial chaperones and, ultimately, the promotion of anti-aging and proteostasis effects [69]. The REMSF exposure utilized here is a potential new strategy to treat age-related diseases such as Alzheimer's. We will examine the experiments from REMFS exposures in human neuronal cultures [40] and the studies from other investigators in AD mouse models [41].

4.1.2 REMFS in human neurons

One of the hallmarks of the aging process is the decrease of the proteostasis due to attenuation of the HSF1 which produce protein aggregation [42]. Alzheimer's is the most common protein deposition disease, it is caused by beta amyloid (Aβ) aggregation. Our recent study showed that REMFS decreased Aβ levels in human neuronal cultures [40]. REMFS decreased Aβ 1–40 and Aβ 1–42 levels. Importantly, it did not cause any toxicity in the neuronal cultures. We tested several REMFS parameters such as time of exposure, frequency, etc. to define any change in the levels of Aβ. Initially we used REMFS treatments at 64 MHz with a SAR of 0.6 W/kg daily for 1 h for 21 days. Results showed a decrease of 58.3% in Aβ 1–40 levels. We also found that these treatments did not cause any toxicity to the cultures compared to control, non-treated cells as measured by LDH levels, cell morphology, cell attachment, cell number, or neurite extension. Subsequently, we decided to determine if 14 days of REMFS at 64 or 100 MHz with a lower SAR of 0.4 W/kg also decreased the Aβ 1–42 levels. We found that there was a similar significant difference in the Aβ 1–42 levels when we increased the exposure time from 1 to 2 h or when we put the chamber outside the incubator. When we increased the frequency from 64 to 100 MHz; we found a similar beneficial effect in Aβ 1–42 levels. This suggest that REMFS at 64 MHz with a SAR of 0.4 W/kg for 1 h could be the minimal energy required to induce reduction of the Aβ peptides levels, these results are important for future clinical trials. All these suggest that the decrease of Aβ levels in cell cultures were mediated by the activation of the proteostasis master regulator HSF1 [39], this activated HSF1 would increase the expression of chaperones to induce Aβ degradation.

4.1.3 REMFS in AD mouse models

The first REMFS study that prevented cognitive impairment in a transgenic (Tg) AD mouse model "Transgene with human APP gene bearing the Swedish mutation" (AβPPsw) was performed with a pulsed/modulated RF-EMF at 918 MHz which produced a SAR of 0.25–1.05 W/kg over a 7–9 month period [41]. Non-treated Tg mice showed cognitive impairment in memory tests, on the other hand treated Tg mice preserved memory after 6–7 months of REMFS treatment. A more recent REMFS experiment applying daily exposures for a two-month period in older Tg mice (21–27 months) showed improvement in the Y-maze task (memory test), though did not show improvement in more complex tests after 2 months of REMFS [36]. Also the old non-treated Tg had very high levels of Aβ deposition in most areas of the brain. Conversely, the EMF-treated Tg mice exhibited an impressive 24–30% removal of Aβ deposits, suggesting a disaggregation of pre-existing Aβ deposits following 2 months of daily EMF treatment. More importantly, these long-term (daily for up to 9 months) exposure schedules were found to be very safe because they did not demonstrate any harmful effects including, no effects on brain oxidative stress or abnormal brain histology, no significant brain heating, no damage to DNA in circulating blood cells, and no gross changes to peripheral tissues. Another study performed at a higher frequency (1950 MHz, SAR 5 W/kg, 2 h/day, 5 days/week) was also found to ameliorate AD pathology in Tg-5xFAD and wild type (WT) mice exposed to REMFS for 8 months [38]. Remarkably, long-term REMFS significantly decreased not only Aβ plaques, APP, and APP carboxyl-terminal fragments in whole brain (including hippocampus and entorhinal cortex), but also inhibited the parenchymal expression of beta-amyloid precursor protein cleaving enzyme 1 (BACE1) and neuro-inflammation. Additionally, REMFS recovered memory impairment in

AD mice. Furthermore, treated Tg showed expression of 5 genes (Tshz2, Gm12695, St 3 gal1, Isx and Tll1), which are associated with Aβ metabolism. We found that these genes are significantly altered inTg-5xFAD mice, showing diverse responses to the treatments in the hippocampus of wild control and transgenic mice. Treatment in wild type mice showed no difference than control Tg. Conversely, REMFS-treated Tg group showed contrasting gene expression arrays. All these findings suggest REMFS treatments positively alter Aβ deposition and metabolism in AD, but not in wild type mice [38].

Together, human neurons and AD model mouse experiments suggest that REMFS exposures decrease Aβ at the extra and intra cellular levels. Different from the clinical trials with active and passive immunization, REMFS did not cause encephalitis or inflammation. REMFS has important effects in preventing and decreasing brain Aβ deposition, therefore making REMFS a potential therapeutic strategy in the treatment of advanced AD patients who have massive Aβ aggregation in the brain.

4.1.4 REMFS potential therapeutic strategy

Considering the REMFS effects in Tg AD mice, the results on primary neuronal cultures are very promising as the REMFS parameters such as frequency and SAR we applied creates an appropriate and safe potential new therapeutic strategy for human exposures. However, before we exposed humans to this type of RF radiation, we need to recognize that extrapolating effects of mice exposure to effects of human exposure is complex. The mouse's geometry, size, tissue penetration, tissue dielectric properties are significantly different from that of a human and therefore the external fields produced during the 915 MHz exposure would result in quite different internal fields. Internal fields are the electromagnetic fields inside the object, and not the electromagnetic fields incident upon the object. The energy absorbed by an object is directly related to its internal field. Consequently, it is imperative to determine what type of external fields could yield the same internal fields in mouse and human. An important EMF parameter to contemplate is tissue penetration; we should consider that tissue penetration is inversely proportional to the EMF frequency. For example, 918 MHz (frequency used in mouse experiments and cell phone) has a skin penetration of less than 4 cm in a human head, while it is a whole-body exposure for a mouse. Human head thickness for an adult male is around 19.4 cm, so to irradiate the center of a human head the exposure should have a skin penetration of minimum of 9.7 cm. This demonstrates that the 918 MHz frequency is not able to reach important deep brain areas such as the hippocampus. Additionally, 918 MHz produced a greater energy than REMFS, so rising the thermal injury risk. Instead, REMFS exposure (64 MHz) has a skin penetration of 13.49 cm, similar to the 14.5 width of a human head making it suitable for a human head.

Using similarities in dosimetry between cell cultures, animal exposure, human phantom exposure, and computer simulation it is possible to adjust conditions for human exposure [70]. Thus, we used frequencies more suitable for human exposures (50–75 MHz). The basis for these frequencies was:

1. MRI machines has been used 64 MHz for several decades giving a safe exposure that is similar to the 50 and 64 MHz used in our previous experiments [39].

2. It is similar to the human whole body resonant frequency (75 MHz), [71] at this frequency the body absorbs up to 10 times as much as power as when it is not in

resonance [72]. Consequently, we would need to apply less power and achieve the minimum SAR that could achieve biological effect, a safer exposure compared to high energy fields. This would decrease the complexity of the EMF-biological system interaction decreasing the heat production from the exposure.

The physical and biological conditions of the exposed target would affect the EMF parameters of the exposures concerning the case under study [73].

3. Our REMFS exposures produced a SAR (0.4–0.9 W/kg) well below the value limits values of 2 W/kg set by the Institute of Electrical and Electronics Engineers (IEEE) [40], so offering a safe framework for clinical trials [39]. The REMFS parameter for human exposures will range from daily to twice weekly, with a length extending from 30 min to 1 h for several months founded on human neurons and AD mouse studies [36, 37, 39–41].

4.1.4.1 REMFS anti-aging effects

In our previous studies, we determined that REMFS enhanced the HSF1-DNA and delayed the aging process. Taking into consideration that the decline in proteostasis is the earliest event in the aging process and that it is caused by attenuation of the HSF1-DNA binding [66, 74], this makes REMFS a potential therapeutic strategy to treat age-related diseases.

Nevertheless, we should take into consideration other pathway imbalances that cause the pathomolecular mechanism of age-related diseases. Take, for example, the Forehead box protein (FoxO) pathways whose dysregulation results in accelerating the aging process [75]. This suggests that delaying the aging process may be achieved by reactivation of both HSF1 and FoxO pathways (longevity pathways). The combination of the treatments for these two pathways such as HSF1 enhancers (REMFS) in combination with caloric restriction mimetics such as resveratrol (RV) would be an appropriate therapeutic strategy [69, 76]. Enhancing these two pathways that control an array of different processes, including metabolism, cognition, stress response, and brain plasticity demands close monitoring to prevent hyperstimulation of either pathway, thus controlling side effects [69]. For this reason, we suggest using REMFS because 64 MHz affords a safe framework for human treatments [77]. Our previous studies utilized a non-ionizing EMF radiation of 50 MHz allowed safe exposures comparable to our recent study in human neurons with 64 MHz [39]. We should take into consideration that 918 MHz has less skin penetration and therefore the energy carried by the exposure is absorbed adjacent to the skin. In an interest study the RF exposure during 30 min with a 2.7–4 W/kg SAR, versus a 16 min with 6 W/kg both caused a noteworthy temperature change (0.1–0.4°C), as well as other physiological changes in heart rate, localized sweating, and blood flow [78], thus, we suggest lower and effective SAR values (0.4–0.9 W/kg) to prevent these side effects. REMFS can be applied through different exposure systems such as antennas in anechoic chambers or large TEM chambers, these chambers would likely about 10 m in length, 6 m in height, and 6 m in width and utilized frequencies between 50 and 64 MHz [79, 80]. The Institute of Electrical and Electronics Engineers (IEEE) recommend maximum permissible exposure (MPE) values of less than 1 W/kg [81]. Our REMFS treatment produce SAR's under this limit, so suggesting that this is a safe exposure for human treatments. An important aspect to consider is the homocysteinylation of the HSF1 which could be the cause of the age-related attenuation of the HSF1-DNA binding. Therefore, decreasing plasma homocysteine levels by dietary interventions is recommended to prevent the HSF1-DNA binding [82].

Likewise, FoxO activation is a very crucial part of the combination therapy to delay the aging process and age-related diseases. RV is one of the most effective FoxO activators; it has few side effects and it is easy to administer. RV also activates the mTOR, and SK1N pathways [83]. RV has effects on multiple pathways such as antioxidant, vasodilating, inflammation, cell growth, atherosclerosis, anticoagulant, and beneficial for the cardiac rhythm. Notably, RV decreases mortality and metabolic syndrome in high-calorie and high-fat diets in mice experiments [84]. For these reasons RV is a potentially a new therapeutic strategy to prevent and treat metabolic syndrome and diabetes mellitus type II. One disadvantage is that RV bioavailability is poor as a consequence of metabolic alterations in the plasma. Hypothetically, REMFS combines with RV as soon as a decline in any of these two pathways is detected. One of the methods to determine if the HSF1 pathway is failing would be monitoring the T lymphocyte HSF-1 DNA binding [69]. The method to detect a decline in the FoxO pathway includes testing the FoxO3a binding to DNA. An important part of the evaluation is to determine the aggregation of beta amyloid (Aβ), Tau, or α-synuclein proteins in the human brain using Positron-emission tomography (PET) scanning to monitor neuro-degeneration and protein deposition load [69, 85].

4.1.4.2 REMFS in Alzheimer's disease and other protein aggregation diseases

While REMFS might affect the organism in a whole-body basis, we also consider that more focused exposures, individual body targets may be selected. Any organ that shows functional decline, including the brain, kidneys, joints, liver, or heart, may benefit from engineered REMFS to induce protein disaggregation by activation of the HSF1 pathway. Therefore, we will initiate human head exposure to treat the most common cause of dementia (Alzheimer's disease). Before clinical trials are considered we have to determine the best electromagnetic settings for human exposures such as power output, power deposition, far field, antenna type, distance from antenna, electric field, magnetic field, etc. that will produce uniform internal fields similar to our previous studies when applied to a human brain with a target SAR of 0.4–0.9 W/kg [40]. Initially, we determined by mathematical and computer modeling that the REMFS exposures in our biological studies delivered a safe thermal and SAR measurements [70]. With these results we developed a virtual exposure system by numerical model and computer simulation. We designed a virtual antenna that delivers a SAR of around 0.6 W/kg to a simulated phantom of a human brain. With these simulations we found the REMFS parameters that would deliver a uniform radiation to a human skull in clinical trials [86]. In the near future, we will experimentally confirm these results using an appropriate antenna to expose a Specific Anthropomorphic Mannequin (SAM) human head phantom [87] with internal and external probes oriented vertically to determine the EMF parameters that will provide an effective and safe SAR for future Alzheimer's treatment. Data suggest that the ideal environment for these treatments should be an anechoic chamber to prevent RF wave reflections and provide a uniform exposure to the subjects. The final step will be to initiate phase 1 clinical trials in patient with early Alzheimer's disease to determine safety and efficacy of this new potential therapeutic strategy.

5. Future diagnostic procedures

We performed several computer modeling and simulation to create visual representations of the interior of the human body for diagnostic analysis, as well as visual representation of the function of some organs or tissues. We utilized

EMF of different frequencies up to 5 GHz because they are commonly used in medicine for diagnosis. Here, we show several future non-invasive EMF diagnostic procedures.

5.1 Pathological bone

We performed microwave and thermal simulation of human bone. The results showed differential power dissipation over the bone materials with different temperatures within 2–4° change for various frequencies [88]. This simulation also showed the distinction between normal and abnormal bone tissues, indicating that this is an effective method for diagnosing normal bone and pathological bone including bone cancer, fractures and infection.

5.2 Femoral neck vasculature

We also performed simulations of the vasculature of the femoral bone [89]. Disruption of the blood supply to the femoral neck is a well-recognized source of morbidity and mortality, often resulting in avascular necrosis of the femoral head. EM simulations of femoral neck fractures were presented as examples. Electric fields were generated in a fashion that exploited disruptions within the vasculature of the femoral neck. Simulated blood vessels were developed in two-dimensions: the phi direction (the circular), and the z-direction. Two different frequencies, 3 and 5 GHz were considered, with 100-J energy pulses within blood vessels of 2.54 mm in diameter. The fat surrounding the bone was simulated, we also developed an additional model with layered fat and skin above the vessels. We were able to visualize the femoral neck's blood vessels. This research validated the technique of detecting and diagnosing pathology of the circulation of femur bone in humans. The approach using the characteristics of the RF response of the reflected power at various frequencies as determined from the finite element simulation was appropriate, and it fits well with the practical model if implemented via MEMS (micro-electro-mechanical systems). Magnetic sensors may be built on flexible substrates in order to shape up the sensors and make them suitable for measuring various sizes. The COMSOL models were made close to the anatomical model seen in **Figure 2**. It shows the head, neck, and leg of the femur. The exploitation of electric field indicates the feasibility of a subsequent practical model to diagnose femur vasculature pathology including avascular necrosis of the femoral neck and other human bones.

5.3 Arteriosclerosis disease

We lastly performed simulations to detect arteriosclerosis of human blood vessels which is associated with coronary artery and peripheral vascular disease. Our laboratory developed a new non-invasive EMF approach for the diagnosis of stenosis/arteriosclerosis disease. A simulated human foot was analyzed using COMSOL multi-physics software in attempt to visualize, analyze, and quantify the degree of peripheral vascular disease, which plays a pivotal role in the development of diabetic foot ulcers. The simulation results served as a proof of concept for predicting and stratifying certain degrees of occlusion within the peripheral vasculature. Although this study was based on computer modeling with simulation results in nature, the research parameters shows promise for practical models for future diagnosis of the peripheral vasculature via EM parameters. The study shows promises for the practical implementation of the device. Current technologies with MEMS/NEMS can serve as hardware systems

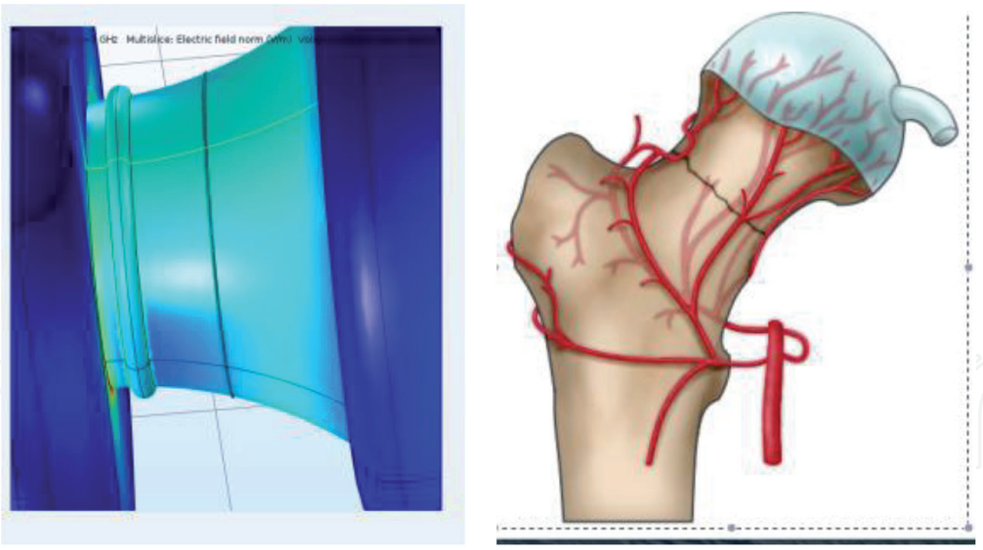

Figure 2.
(a) The computerized model of the femur (b) The anatomical femur with components and blood vessels: blood vessels showing rupture in the femur vasculature.

proper for this diagnosis process designed for detecting EM parameters needed for the diagnostic tool for the early detection of peripheral vascular disease, and ultimately, diabetic foot ulcers [90].

6. Conclusion

Since the discovery of electromagnetic fields, the beneficial health effects and their potential applications toward the treatment and diagnostic of age-related diseases has been eagerly sought with promising results. The effect of non-thermal, non-ionizing REMFS has been examined in our laboratory for its ability to induce cytoprotecting effect via the heat shock factor-1. Results suggest anti-aging effects occurred as a direct consequence of a biological systems-REMFS interaction, and herein we have proposed a quantum tunneling-based mechanism mediated by the interfacial water to explain it. Our pioneering studies have also demonstrated safe REMFS decreases toxic Aβ levels in primary human brain cell cultures; an outcome likely resulting from increased Aβ degradation. When considered in parallel with several transgenic AD mouse model studies that have demonstrated the efficacy and safety of REMFS in-vivo to induce removal/disaggregation of pre-existing Aβ deposits and prevent or reverse cognitive impairment, the potential application of REMFS toward the treatment of AD and age-related protein deposition diseases is certainly encouraging. Furthermore, the simultaneous modulation of longevity pathways through HSF1 enhancers (e.g., REMFS) and FoxO pathway up-regulators (caloric restriction mimetics, such as resveratrol) suggest complementary strategies could act synergistically to balance and preserve cellular defense and repair systems. As REMFS targets the most important pathways affected in Alzheimer's disease and other age-related pathologies, HSF1 modulation and enhancement by REMFS could potentially restore a variety of damaged signaling networks associated with the aging process, additionally, diagnostic EMF devices could prove to be a fast, non-invasive, and painless tool that will avoid incisions into the body and the removal of tissue for diagnosis of a multitude of diseases.

Acronyms

EMF	electromagnetic fields
REMFS	repeated electromagnetic fields stimulation
SAR	specific absorption rate
HSF1	heat shock factor 1
HB	hydrogen bond
FLIFW	first layer of the interfacial water
GRNA	guanine of the RNA
O	oxygen
HSP	heat shock proteins
HSR1	heat shock RNA
RV	resveratrol
FoxO	Forkhead box protein
Aβ	amyloid beta
AD	Alzheimer's disease
SOD	superoxide dismutase
WT	wild type
Tg	transgenic

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